



Myasthenia Gravis in Pregnancy Treated With Daily Massive Vitamin D Dose

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Abstract

Myasthenia gravis (MG) is an autoimmune disease affecting the motor endplate of striated muscle. It is caused by antibodies that act in the cholinergic receptors at the post-synaptic portion of the neuromuscular junction, which results in asthenia and fatigue in some muscle groups. In pregnancy, it's unpredictable, because pregnant women can present MG exacerbation, remission, stability, or even a myasthenic crisis during pregnancy. Complications are more frequent in the first trimester of pregnancy and the first 30 days of puerperium. Vitamin D and its metabolites are potent immunomodulators since their immuno-regulatory effect directly inhibits effector T cells and induces regulatory T cells (Treg) to decrease the production of inflammatory cytokines. The authors present a case report of a patient with MG who was treated throughout pregnancy with massive doses of vitamin D, obtaining good results.

Keywords

Myasthenia gravis, Autoimmune, Vitamin D, Asthenia, Fatigue

Introduction

Myasthenia gravis (MG) is an autoimmune disease affecting the motor endplate of striated muscle. It is caused by antibodies that act in the cholinergic receptors at the post-synaptic portion of the neuromuscular junction, which results in asthenia

and fatigue in some muscle groups. The annual incidence of MG in the world reaches 1-2 per 100,000 individuals; it is more prevalent in women (3:11 ratio) [1].

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Antibodies against acetylcholine receptors (AChR) in the neuromuscular junction (NMJ) are likely accountable for damages to neuromuscular transmission, among other factors. Viral or bacterial infections that modify the motor endplate surface are another factor possibly causing such damages, since they make it immunogenic, as well as viral or bacterial antigens that would allow a cross immune response likely affecting NMJ when they share epitopes with acetylcholine receptors. Therefore, neuromuscular transmission destruction possibly occurring through antigenic modulation damages the complement-mediated synaptic membrane; assumingly the functional blockade of AChR sites can explain the causes of MG [2,3].

Asthenia and fatigue are MG clinical features, mainly at repetitive activity, although these symptoms decrease after a period of rest. Thus, exercising, emotional stress, infections, medicines, high temperatures, and even pregnancy can worsen muscular weakness. Levator palpebrae superioris and extraocular muscles are the muscles most commonly affected by MG, which can cause eyelid ptosis and asymmetrical ocular paralysis (resembling other ophthalmological pathologies). Besides, MG also affects proximal member, facial and neck extensors, and impairs chewing and swallowing, leads to weight loss and dysphonia by weakening mastication, esophagus, and larynx muscles. The myasthenic crisis is an emergency condition caused by respiratory function worsening due to severe muscle weakening, which prevents the respiratory function or the proper functioning of the airways [4,5].

Myasthenia gravis is unpredictable during pregnancy; pregnant women can present MG exacerbation, remission, stability, or even a myasthenic crisis during pregnancy. Complications are more frequent in the first trimester of pregnancy and the first 30 days of puerperium. Besides, the clinical course of the disease during pregnancy does not allow predicting episodes likely to happen in future pregnancies. Moreover, the transplacental passage of maternal immunoglobulins G can also result in neonatal myasthenia gravis [6-9].

The prognosis and life expectancy of myasthenic patients have improved and respiratory failure is rare in properly treated patients because of the currently available treatments, with emphasis on corticosteroids, intravenous immunoglobulins, and acetylcholinesterase inhibitors; however, pregnancy limits the use of many medicines. Immunosuppressants, such as methotrexate, cyclophosphamide, and mycophenolate mofetil are contraindicated in pregnancy. Corticosteroids, azathioprine, and cyclosporine should be avoided in patients with mild symptoms, but are an option for individuals who do not achieve good symptom control with anticholinesterase drugs, alone. On the other hand, high azathioprine and cyclosporine dosage can lead to spontaneous abortion, preterm birth, low birth weight, and chromosomal and hematologic changes. Plasmapheresis and high doses of intravenous immunoglobulins are only used in cases when conventional therapy fails or during a myasthenic crisis, resulting in variable outcomes [8-11].

Vitamin D and its metabolites are potent immunomodulators [12,13] since their immunoregulatory effect directly inhibits effector T cells and induces regulatory T cells (Treg) to decrease the production of inflammatory cytokines. Previous studies have already reported that patients with autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis [12-14], have low vitamin D levels. A research conducted in 2018 showed that patients with MG had lower vitamin D (25 (OH) D) dosage (18.8 ± 8.4 ng/mL) than healthy individuals in the control group (26.3 ± 6.1 ng/mL) ($p < 0.05$) [14]. Vitamin D₃ can modulate the Treg-related suppression capacity in the acetylcholine receptor (AChR). Based on such outcomes, some studies used massive Vitamin D doses (80,000 IU/day) to treat MG. The ability to silence or express genes, immune modulation, and inflammation suggest the potential role of vitamin D as medicine to treat autoimmune and inflammatory diseases given its positive effects, mainly on the immunologic system [15-17].

Vitamin D level increase during pregnancy is a physiological way to optimize fetal skeleton formation. However, studies that have assessed the risk of using

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vitamin D in pregnant women are scarce. The benefits of such a treatment seem important, mainly in patients whose treatment with usual medications fails. However, some side effects, such as hypercalcemia, cardiac arrhythmias, and kidney stones, have been reported. Authors of the current study herein report the case of a patient who initiated prenatal care in their clinic and who was already taking massive vitamin D doses to treat MG.

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The clinical case described is that of a young patient, with MG and a history of several treatments without success. For some years, he has been using vitamin D supplementation with massive doses with good disease control. In pregnancy, she used a high dose of vitamin D and that was the biggest concern. There are few reports of this treatment in pregnant women, but considering the importance of maternal clinical stabilization, we chose to maintain the treatment during prenatal care.

CM, aged 38 years, G2P0A1 in the first trimester of pregnancy attended regular prenatal care appointments. She was diagnosed with MG at the age

of 20 years and was treating it with 80,000 IU of vitamin D. She underwent laparoscopic thymectomy in 2002 and had a myasthenic crisis in 2006 - when intubation was needed. Intubation resulted in many complications (pneumonia, pleural effusion) and 60 days of hospitalization; later on, she underwent an open thymectomy. The patient was not responding to the usual treatment as expected and her respiratory condition worsened in 2017. Her treatment history showed the use of azathioprine, cyclosporine, rituximab, mestinon, and plasmapheresis. The patient opted for trying the alternative treatment with 80,000 IU of vitamin D, on a daily basis. The patient did not have any crisis after the beginning of this new protocol and continued to use a daily dose of 80,000 IU of vitamin D during the pregnancy. Vitamin D dose was reduced to 60,000 IU (on a daily basis) in the last trimester of pregnancy due to the dosage of parathyroid hormone (PTH).

The patient started prenatal care at 6 weeks of pregnancy. She was diagnosed with an inevitable miscarriage and was subjected to MVA in the eighth week of pregnancy. At this point, the patient was taking 80,000 IU of vitamin D + Prednisone 5 mg +

Table-1: Laboratory Exams of the Assessed Patient

Exam	First Trimester		Second Trimester		Third Trimester	
Hb (g/dl) / HTC (%)	13.5	39	12.1	35	13.1	39.2
HBsAg	Negative		Negative			
Toxoplasmosis	IgM neg	IgG pos	IMMUNE		IMMUNE	
Rubella	IgM neg	IgG pos	IMMUNE		IMMUNE	
CMV	IgM neg	IgG pos	IMMUNE		IMMUNE	
Anti- HCV	Negative		Negative		Negative	
Anti- HIV	Negative		Negative		Negative	
Ferritin	105.2		67.9		55	
VDRL	Negative		Negative		Negative	
ABORh	A+					
Urine culture	Negative		Negative		Negative	
25Oh Vit D	>155.9		>155.9		> 155.9	
Glucose (mg/dl)	79		78		76	
FT4/TSH	0.8	3	0.8	0.67	0.7	1.8
OGTT75g			Fasting	73		
			1h	150		
			2h	113		
Parathyroid hormone (pg/ml)			9			

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vitamin complex (folic acid + zinc and B12 / B6) daily. The patient underwent a thrombophilia examination 2 months after the miscarriage and presented a low C protein level (32%). The exam was repeated and confirmed the low C protein (21%) levels and plasminogen activator inhibitor (4G/5G). The results of the other exams were regular (**Table-1**).

On July 1, 2019, the patient attended a new medical appointment, she presented menstrual delay and positive hCG; she was 4/5 weeks pregnant. Treatment started with enoxaparin at a dose of 40 mg/day; the daily vitamin D dose of 80,000 U and multivitamins

was kept. ASA 100mg/day was included in the treatment at the 12th week of pregnancy due to collagenosis. **Fig-1** shows the blood pressure (BP), uterine height (UH), and weight evolution. The ferritin level of the patient was low in the third trimester of pregnancy and she presented intolerance to oral iron repletion. The choice was made to start venous treatment with ferric hydroxide (100mg / 5ml - 1 vial) at a dose of 200 mg (2 vials) diluted in 100 ml of saline solution for three consecutive weeks, which led to the recovery of the iron levels. **Table-1** shows the results of laboratory tests and **Table-2** presents the result of the patient's ultrasounds.

Table-2: Imaging exams of the assessed patient

Exams	
First trimester obstetric US	1.5 x 1.1 cm gestational sac, compatible with 4/5-week gestation
First trimester nuchal translucency US with uterine arteries Doppler	12:3-day gestation, nasal bone present, NT = 1mm; RURI = 0.44; RUPI 0.62; LURI 0.38; LUPI 0.5
Morphological USG	No evidence of morphological changes - Performed at 23 weeks, uterine Doppler in the second trimester of pregnancy without abnormalities, MPI = 0.88, absence of notch in uterine arteries.
Fetal echo	No changes in fetal heart morphology or heart rate.
Obstetric USG with umbilical and middle cerebral arteries Doppler	Normal amniotic fluid, C/U <1.0; single fetus in cephalic presentation, with posterior dorsal and good fetal movement. Gestational age of 33 weeks

(RURI - right uterine artery resistance index; LURI - left uterine artery resistance index; RUPI= right uterine artery pulsatility index; LUPI: left uterine artery pulsatility index; C/U = cerebral-umbilical ratio; NT = nuchal translucency; US - ultrasound)

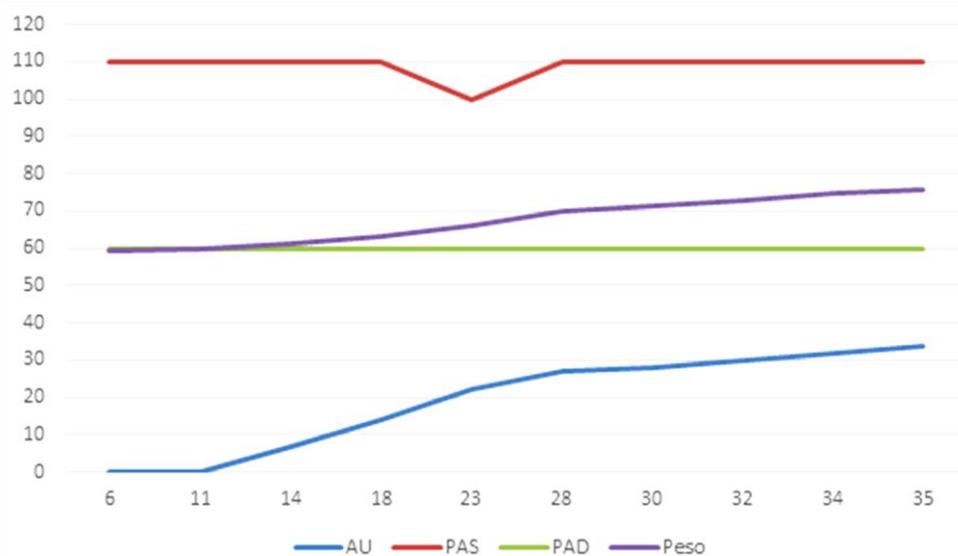


Fig-1:

AU (uterine height), PAS (systolic blood pressure), PAD (diastolic blood pressure) and Peso (weight evolution of the assessed patient)

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The patient had uterine contractions on the 36th week of pregnancy and was hospitalized for clinical control. Urine gram and complete blood count (CBC) were regular. The patient evolved to labor and was subjected to a cesarean section, at the 36th week of pregnancy. A male fetus was extracted, he weighed 2,550g and was in good health condition; he was sent to isolation with his mother. The newborn is currently being breastfed, he presents good health condition and reported regular results in the puerperal examination performed at 7 and 40 days postpartum. Enoxaparin delivery was suspended 6 weeks after childbirth and the dose of 60,000 IU of vitamin D/day (controlled by the PTH) multivitamin with iron was maintained. The baby was treated with natural breastfeeding ad libitum; he remains under follow-up with a pediatrician and did not present any clinical complications.

Discussion

Pregnant women with myasthenia gravis can have exacerbation, remission, or even no disease change throughout pregnancy. Women are recommended to delay pregnancy for at least two years after having contracted MG, since maternal mortality rate is inversely proportional to disease duration. Besides, it is important to establish an MG treatment that can balance pregnant women's good clinical conditions to fetus safety [9]. However, it is hard achieving such an aim through conventional treatment, since several medicines pose high teratogenicity risk and damage fetal development. Therefore, drugs protocolled to treat MG in pregnant women, such as pyridostigmine, use to be acetylcholinesterase inhibitors [18,19].

Vitamin D is a good alternative-treatment option, mainly for patients refractory to conventional treatment, even when it is not the first choice. Current guidelines for vitamin D use are restricted to the usual dose applied for treatment repletion [20]. However, high doses of vitamin D seem to be effective in treating several autoimmune diseases, including myasthenia gravis, due to the strong immunomodulatory effect of its metabolites. The massive dose therapy remains an open field for new research due to dose heterogeneity, which often ranges from 80,000 to 120,000 IU/day [16,17].

The herein reported patient went into labor at 36 weeks of pregnancy; she was subjected to cesarean section due to the recommendation of the obstetrician. There are no contraindications to vaginal delivery or labor induction in MG patients; however, the cholinergic receptors of the neuromuscular junction are the target of antibodies, which leads to voluntary strength decrease at the time of delivery [1]. Besides, there is no consensus in the literature about the frequency of preterm labor (PT) or about low birth weight [21,22].

The major concern of the research group was the repercussions caused by high vitamin D levels in the fetus and the future newborn. However, fetus development was extremely favorable, he did not record a growth pattern deficit. There was no placental calcification, deviations in amniotic fluid volume, or renal calcification in the fetus. It is important reminding the case of a family that was intoxicated by massive vitamin D doses due to the intake of food cooked in nut oil. All family members presented symptoms of hypercalcemia; after eleven years, the renal biopsy of one of them showed persistent nephrocalcinosis [23]. There are reports about two infants (aged 2 and 18 months), from different families, who were intoxicated by vitamin D because they were administered with the wrong dosage of it by family members. The identified clinical symptoms were nausea, vomiting, polyuria, dehydration, reduced muscle tone, hypercalcemia, hypercalciuria, and impaired renal concentrating ability [24].

Vitamin D concentration in breast milk depends on maternal vitamin level and it is usually not enough during regular maternal repletion. Although the herein reported patient took massive vitamin D doses on a daily basis, her newborn did not have nausea, vomiting, or polyuria; he showed good growth patterns, functional development compatible with his age, and adequate muscle tone. The alternative treatment used by the patient a few years ago is based on the Coimbra Protocol. This protocol consists, briefly, in the use of high doses of vitamin D for the treatment of autoimmune diseases, associated with some supplements such as magnesium, omega-3, and a vitamin compound (riboflavin, methylfolate,

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methylcobalamin, choline, selenium, zinc, chrome). It requires monitoring by a qualified doctor and periodic clinical and laboratory controls, to define the ideal individualized dose according to each patient and pathology in question. It includes a restrictive calcium diet, in addition to generous hydration (about 2.5 liters/day), to control calcium and kidney function. The daily doses currently vary between 50,000UI and 300,000UI [25].

Now, at the age of 4 months, the baby is weighing 7400g. Follow up with a pediatrician remains in course, but there is no sign of transient neonatal myasthenia, so far. Newborn reflexes were normal. The mother is in good health, maintaining the same protocol and treatment.

Conclusion

Treating pregnant women with myasthenia gravis with high vitamin D doses did not cause immediate changes to the conceptus. Long term complications must be assessed with follow-up on this newborn.

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