ORIGINAL ARTICLE

Myasthenia Gravis and Pregnancy: Toronto Specialty Center Experience

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ABSTRACT: ***Background:*** Myasthenia gravis (MG) is an autoimmune disorder that frequently affects young women of reproductive age. The multidirectional interplay between MG, pregnancy, and fetal health poses a complex scenario for pregnant women with MG and the healthcare team. Here, we reviewed our local experience with MG, pregnancy, and outcomes. ***Methods:*** We performed a retrospective chart review of patients with MG attending the Prosserman Family Neuromuscular Clinic from 2001 to 2019 and who were referred to a high-risk pregnancy clinic. MG status was defined as stable, better, or worse. Information was collected on the delivery route, pregnancy, and neonatal complications. ***Results:*** We identified 20 women with MG for a total of 28 pregnancies. Worsening was observed in 50% of pregnancies: 18% during pregnancy, 25% following delivery, and 7% during both. 66.7% of patients with MG duration of 2 years or less had worsening during pregnancy. Three patients who stopped immunosuppressive treatment during pregnancy worsened and one had a crisis. C-section was done in 29% of pregnancies. The rate of delivery complications was 7% and of neonatal MG was 7%. ***Conclusion:*** A high proportion of MG patients worsened during pregnancy, particularly those with disease duration less than 2 years, and those who discontinued immunosuppression during pregnancy. However, pregnancy was largely unaffected, rate of neonatal MG was low, frequencies of C-section, delivery complications, and premature births were similar to the general population. While the study has limitations due to the retrospective nature, these insights provide some guidance when counseling young myasthenic women about family planning.

RÉSUMÉ : Myasthénie et grossesse : une expérience menée dans un centre hospitalier spécialisé de Toronto. ***Contexte*** **:** La myasthénie est une maladie auto-immune qui affecte fréquemment les jeunes femmes en âge de procréer. Les multiples aspects réciproques qui existent entre cette maladie, le fait d'être enceinte et la santé du fœtus finissent par composer un panorama complexe pour les femmes enceintes qui sont atteintes de myasthénie ainsi que pour les équipes soignantes. Nous voulons donc ici revenir sur notre expérience avec ces patientes et sur l'évolution de leur état de santé. ***Méthodes*** **:** Pour ce faire, nous avons effectué une analyse rétrospective des dossiers de patientes atteintes de myasthénie qui ont fréquenté la *Prosserman Family Neuromuscular Clinic* de 2001 à 2019 et qui avaient été orientées vers une clinique spécialisée dans les grossesses à haut risque. L'état de la myasthénie chez ces patientes a été défini de la façon suivante : « stable », « s'est amélioré » ou « s'est aggravé ». Nous avons également recueilli des renseignements quant à leur grossesse, au travail ayant mené aux accouchements (*delivery route*) et à des complications néonatales. ***Résultats*** **:** Nous avons identifié 20 femmes atteintes de myasthénie ainsi qu'un total de 28 grossesses. Une aggravation de l'état de santé des femmes enceintes a été observée pour 50 % d'entre elles (18 % pendant leur grossesse ; 25 % à la suite de leur accouchement ; 7 % dans les deux cas). Il est à noter que 66,7 % des patientes dont la myasthénie durait depuis 2 ans ou moins ont vu leur état de santé s'aggraver en cours de grossesse. Plus encore, 3 patientes qui avaient cessé un traitement immunosuppresseur pendant leur grossesse ont vu leur état de santé s'aggraver alors qu'une autre a subi une crise. Pour l'ensemble des grossesses, il est à noter que 29 % d'entre elles se sont terminées par césarienne. Enfin, le taux de complication des accouchements a été de 7 % tandis que celui des cas de myasthénie néonatale a été également de 7 %. ***Conclusion*** **:** Une part importante de patientes atteintes de myasthénie ont donc vu leur état de santé s'aggraver en cours de grossesse, particulièrement celles dont la maladie durait depuis moins de deux ans et celles qui avaient interrompu un traitement immunosuppresseur. Cela dit, les grossesses n'ont pas été, dans une grande mesure, affectées par cette maladie. Qui plus est, le taux de myasthénie néonatale s'est avéré faible alors que les taux de césarienne, de complications à l'accouchement et de naissances prématurées se sont révélés semblables à ceux de la population générale. Bien que cette étude présente des limites en raison de sa nature rétrospective, ces constatations pourraient être utiles au moment de prodiguer des conseils en matière de planification familiale à des jeunes femmes atteintes de myasthénie.

Keywords: Myasthenia gravis, Pregnancy, Outcomes, Complications, Management

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Introduction

Generalized autoimmune myasthenia gravis (MG) preferentially affects young women of child-bearing age.[1,2] Concerns in this patient population include family planning and the safety of pregnancy in MG, the effects of pregnancy on MG control, complications at the time of delivery and in the immediate postpartum period, and the concerns of teratogenic potential of MG medications including cholinesterase inhibitors,

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corticosteroids, and other immunosuppressants.[3] Our knowledge about MG and pregnancy arises from retrospective reports as MG is rare and prospective studies are lacking. Older literature suggests that immunosuppressive drugs should be stopped in women contemplating pregnancy or who are pregnant, and more recent guidelines advocate judicious use of immunosuppressants.[4,5] The course of MG during pregnancy is uncertain and it has been reported that one-third of patients worsen during pregnancy, but two-thirds remain stable.[6] The risk of disease exacerbation is reported to be higher in the first trimester and postpartum period, with the highest reported risk of exacerbation in the postpartum period at about 30% of patients.[6,7] Additionally, the course of MG may vary in subsequent pregnancies.[8] MG exacerbation may be associated with spontaneous abortion possibly due to placental inflammation caused by autoimmune antibodies and inflammatory cytokines leading to disruption of fetal perfusion.[8,9]

Transient neonatal myasthenia may affect 12–20% of infants born to patients with MG; affected newborns have weakness, hypotonia, bulbar and extraocular weakness, and possible respiratory impairment that can persist for up to 3 weeks.[10,11] Very rarely, a severe myopathy or arthrogryposis multiplex congenita with multiple joint contractures may affect children of MG mothers.[3] In light of these different reports, guidelines about patient education, monitoring and referral to rapid access, neonatal high-dependency care have been developed.[5] We aimed to review our experience with MG and pregnancy at our local MG specialty center.

Methods

We performed a retrospective chart review of patients with MG attending the Prosserman Family Neuromuscular Clinic from 2001 to 2019. The diagnosis of MG was based on the clinical presentation, abnormal single fiber electromyography studies, and the presence of MG autoantibodies, if done. Different methods of MG assessment were done over the years: initially with routine physician's clinical assessment of disease status in all subjects and quantitative myasthenia gravis (QMG) scores. In the last 10 years, the myasthenia gravis quality of life score (MG-QoL 15) (indicates increased disease severity with higher scores),[12] myasthenia gravis impairment index (MGII), (used for assessment of disease severity and used for baseline and follow-up assessments with higher values showing greater disease burden),[13] and the single simple question (SSQ) (reports a patient's perception of their overall MG status with 100% being normal) were also used for patient assessment.[14] Due to the variation in evaluation methods, we classified the MG outcome into stable, improved, or worse based on the patient's report, clinical assessment, and MG score (in use at the time of visit) as documented during the respective clinic visit. The final classification was based on the majority outcome of these parameters, i.e. two out of three. We included both pregnancy and the postpartum period (6 weeks after delivery) as periods for assessment. We considered any patient who had worsening respiratory and bulbar function that required ICU admission as having a myasthenic crisis. Other than demographic factors such as age at pregnancy, acetylcholine/MUSK serology, type of MG (generalized vs. ocular), thymectomy status, and treatment, we also collected information related to pregnancy complications, the delivery route, premature birth, and neonatal complications during delivery including neonatal MG.

Table 1: Demographic data on patients with MG and pregnancy

Twenty-eight pregnancies in 20 women	2001–2019
Generalized MG	20 (100)
AChRAb	13 (77)
MuSK	1 (8)
Mean age at the first pregnancy (Y)	29.7 ± 5.7
Mean duration MG (Y)	5.7 ± 5.9
MG worse	16 (57)
MG worse during pregnancy	7 (25)
MG worsening during pregnancy when duration < 2Y	5 (71)
Odds ratio of getting worse with < 2Y MG duration	3.43:1
MG worse after delivery	9 (32)
MG worse when immunosuppression stopped	3 (100)
Onset MG during pregnancy	1 (5)
Onset MG following delivery	1 (5)

AChRAb = acetylcholine receptor antibody; MuSK = muscle specific kinase antibody, Y = years.
Data are given as *n* (%) or as means ± standard deviation.

Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). We used univariate analysis to explore any associations between demographic variables and treatments and MG status during pregnancy or in the postpartum period. Using contingency tables, we calculated the odds ratio and relative risk for MG worsening either during pregnancy or in the postpartum period when the duration of MG before pregnancy was less than or equal to 2 years; the latter cutoff based on previous reports.[15,16] The study was approved by the University Health Network Research Ethics Board.

Results

We identified 28 pregnancies in 20 patients with generalized autoimmune MG (Table 1) seen in the clinic from 2001 to 2020 with pregnancies dating back as far as 1990. Ten out of 13 (77%) tested patients had elevated acetylcholine receptor antibodies and one patient (8%) had anti-MuSK antibodies. The other 15% were seronegative. The mean age at first pregnancy was 29.7 ± 5.7 years and the mean MG duration was 5.7 ± 5.9 years. Two patients had onset of MG during pregnancy – both in the first trimester and one had onset in the immediate postpartum period. MG was well controlled in 17 patients, active in 5, worsened at time of conception in 1, and diagnosed after pregnancy in 3. The preconception MG status was unknown in two. Pregnancy was planned in all except two pregnancies.

Worsening was observed in 50% of pregnancies: 18% during pregnancy, 25% following delivery, and 7% during both pregnancy and following delivery. All except one patient needed up-titration of treatment, which included increasing the dose of steroid in four, addition of steroid in one, increasing frequency

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of IVIG in four, administering PLEX in three, and only increasing pyridostigmine in one. One patient who had mild worsening was closely followed without any change in medication and had spontaneous improvement. Univariate analysis did not show any significant relationship of MG worsening with age at pregnancy, duration of myasthenia, serology, type of MG, and treatment. In those with MG for 2 years or less, 71.4% had worsening during pregnancy or in the postpartum period. (OR 3.43, [0.65–18.22], RR 1.89 [0.86–3.82]). Two other patients worsened: MG durations were 3 and 9 years. Of the three patients who stopped immunosuppressive treatment (azathioprine) against medical advice during pregnancy, all worsened and one had a myasthenic crisis. Seven women had multiple pregnancies; 6 women had 2 pregnancies and 1 woman had three pregnancies amounting to a total of 15 pregnancies. Seven of these pregnancies had worsening MG, four during the first and three during the second pregnancy. One woman who had three pregnancies, remained stable and had been on PLEX during the first and second pregnancies and received PLEX just before the third delivery, which happened to be an elective C-section. There were no significant differences in presentation or clinical characteristics from those with a single pregnancy.

Regarding MG treatments during pregnancy, 10 (35.7%) of the pregnancies were in patients on azathioprine before pregnancy and 7 (25%) during pregnancy. Prednisone was used in 13 (46%) patients before pregnancy and in 14 (50%) during pregnancy. Intravenous immunoglobulin (IVIG) was used in 4 (14%) before pregnancy and in 6 (21%) during pregnancy. In 25% of the pregnancies, patients took more than one immunotherapy before pregnancy and 8 (28%) during pregnancy. All except five patients had undergone thymectomy before the delivery. In those five patients, threehad MG diagnosed after they became pregnant and in two, thymectomy had to be deferred till after delivery since the pregnancy was unplanned. Myasthenic crises occurred in 14% of pregnancies, including one patient with new-onset MG and one who stopped immunosuppressive medications. Cesarean section was done in 29% of pregnancies: 75% were primary cesarean sections and 25% were repeat sections. There were only 2 (7%) deliveries with complications: one case of postpartum jaundice and one case of nuchal cord. There were 2 premature births (7%) and 2 (7%) cases of neonatal MG. All infants recovered fully without permanent issues. None of the patients in our series had an infant with severe myopathy or arthrogryposis multiplex congenita. Treatment with azathioprine before or during pregnancy did not confer risk to the mother or fetus.

Discussion

Our local experience with MG and pregnancy is consistent with previous reports showing that around one-third to two-thirds of MG patients worsen during pregnancy, particularly those with a disease duration of less than 2 years and those who discontinued immunosuppression during pregnancy. However, we also found that the frequencies of C-section, delivery complications, and premature births were not higher compared to the general population in Ontario and that the rate of neonatal MG was lower than in most reports.[17–19]

The influence of pregnancy on MG and the incidence of pregnancy-associated worsening of MG and its timing are variable across studies. A large retrospective study of the Medical Birth Registry data in Norway identified 135 births in 73 women with MG and found worsening of MG in only 10% of pregnancies.[10] However, more than one-third of patients were not on medication and one-third of the cases of MG were diagnosed after their first delivery suggesting a mild or subclinical form of MG compared with most patients in our study who were being treated in an MG specialty referral center and took at least one immunosuppressant medication. Higher rates of both pregnancy-related (21%) and delivery-related (30%) complications were seen in the Norwegian cohort, perhaps due to the differences in MG therapy in that population.[10] Other smaller studies show variable rates of worsening ranging from 23 to 50%.[9,20–23] The course of MG in pregnancy can be difficult to predict with worsening occurring in any of the three trimesters or in the postpartum period, although similar to our study most women have worsening in the postpartum period.[7]

A few factors have been shown to have some bearing on worsening related to pregnancy. As noted in the literature, we found a high proportion of patients with a duration of MG less than 2 years to have worsening of MG during pregnancy with an odds ratio of 3.49 [0.65–18.22].[15,16] A shorter duration, greater disease severity, and abnormality in repetitive nerve stimulation (RNS) studies are other factors described as predicting worsening of MG during pregnancy.[23] Although a specific recommendation about the timing of pregnancy and disease activity is not available for MG, a stable period of at least 6 months is advised before attempting conception in other autoimmune disorder and this advice may apply to MG as well although “stable” is not defined when this interval is suggested.[5,24] Stopping immunosuppressive treatment during pregnancy in our cohort was associated with worsening MG and a higher risk of crisis lending support to the recommendation that this not be done.[25] Somewhat surprisingly, the risk of cesarean delivery was not increased by MG, but was the same as that in the general population in Ontario of about 29% from 2013 to 2019.[17] Also, the rate of premature delivery was 7%, the same as in general population.[17,19] While the rates of C-section vary in different MG populations with rates as high as 67% in Brazil and 78% in Turkey, other large population-based studies do not show increased C-section rates compared to the general population similar to our study.[9,23,26] These results indicate a wide diversity in the global therapeutic approach to pregnancies in MG patients. As suggested by our data, C-section should be reserved for obstetrical reasons. MG is not an indication for C-section and should not preclude a trial of vaginal delivery.[5,27] We found a lower rate of neonatal MG (7%) than previously reported (12–30% of pregnancies).[18] Factors that influence the incidence of neonatal MG have been controversial with maternal severity and the maternal antibody titers failing to show a consistent association.[3,28] One series reported that maternal thymectomy lessened the likelihood of neonatal MG and a long duration of MG had an inverse association with neonatal MG.[8,16] While the mechanisms by which thymectomy reduce the incidence of MG remain obscure, one factor in our series was that the majority of patients had thymectomy before pregnancy and delivery. In addition to thymectomy, disease management in a specialized MG center might also account for these outcomes. None of the patients in our series had an infant with severe myopathy or arthrogryposis multiplex congenita. Although this could be a reflection of the relatively small sample size, genetic factors have been implicated in these severe

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complications, where in a shared HLA haplotype between mother and neonate, increased the susceptibility for neonatal MG by increasing the immunoreactivity to passively transferred antibody.[3,18]

In summary, our results support that pregnancy is a risk factor for worsening in MG and that stopping immunosuppressive treatment increases the risks of relapse and MG crisis. Despite these findings, vaginal delivery was the main delivery route and the rate of cesarean section was not increased compared to that in the general population. The rate of delivery complications did not appear to be increased, and the rate of neonatal MG was lower than expected. Complications that have been noted in pregnant women with MG include premature rupture of membrane, prolonged labor, which may be attributed to the fatigue of striated muscles and also fetal distress.[9,23,29] However, none of these complications were encountered in our patients.

Being a retrospective study design, the study has a few limitations. The acetylcholine receptor antibody status was not available for all patients and we did not have data on acetylcholine receptor antibody titers, as these numerical levels were not reported in a quantitative manner in previous years. Hence, we cannot comment on any potential association between antibody levels and pregnancy outcomes in MG. We did not record the duration of worsening, and therapeutic interventions in a systematic and consistent fashion and there was a nonuniformity of clinical assessment methods, which limits comparisons in the outcome. We also do not have any data on the number of patients who may have elected not to have children due to their MG status, or on family-supportive care that may have been required following each delivery. Finally, a potential referral bias to our specialty MG center may limit the generalization of our results.

Conclusion

Pregnant women with MG can have successful pregnancies and can be optimistic about outcomes in their offspring. However, their MG status is likely to worsen during pregnancy or just after delivery and this possibility must be considered and discussed with women with MG of reproductive age.

Disclosures

The authors have nothing to disclose.

Statement of Authorship

MA was involved in data collection, writing, editing, and reviewing the article. DM was involved in analysis, writing, editing, and reviewing the manuscript. HK was involved in writing, editing, and reviewing the article. CB was involved in writing, editing, and reviewing the article. MS was involved in writing, editing, and reviewing the article. VB was involved in conceptualization, guiding MA and DM in writing the article, editing, and reviewing the article.

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