Original article

UDC: 616.8 009.1:618.2
doi:10.5633/amm.2022.0303

STUDY ON THE TWO-DIRECTIONAL RELATIONSHIP BETWEEN MYASTHENIA GRAVIS AND PREGNANCY

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Due to the high prevalence of myasthenia gravis (MG) in women of reproductive age, pregnancy in patients with MG is not uncommon. This requires special clinical and therapeutic caution. There is a two-way relationship between MG and pregnancy: Pregnancy can affect the course of the disease, but MG can affect childbirth and the occurrence of postnatal complications. The purpose of our study was to evaluate the clinical course, delivery, and neonatal outcome of pregnant women with the diagnosis of myasthenia gravis. The clinical course of the disease during pregnancy, labor, and postpartum period was reviewed, as well as the neonatal period in the 23 infants born to 15 MG mothers. Spontaneous abortion was observed in two pregnant women (8%) in the second month of pregnancy. One newborn was diagnosed with transitory neonatal MG. There were no stillbirths or physical anomalies. Clinical worsening was recorded during 10 pregnancies (40%), in 8 pregnant women. The clinical course of MG in pregnancy is variable and unpredictable, but pregnancy does not affect the long-term course of MG. Spontaneous abortion is a potential complication in pregnant women with MG. Cesarean section is a more frequent intervention in pregnant women with MG compared to the general population of women. Thymectomy in mothers with MG before pregnancy could potentially have a positive benefit for the newborn. Neonatal transient myasthenia was uncommon in our patient population. No congenital abnormalities were discovered in the 23 babies delivered at our institution.

Acta Medica Medianae 2022;61(3):20-26.

Key words: *myasthenia gravis, pregnancy, clinical course*

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Introduction

Myasthenia gravis (MG) is an antigen-specific autoimmune disease in which antibodies against the nicotinic acetylcholine receptors (nAChR antibodies) or other postsynaptic antigens cause a postsynaptic block of neuromuscular transmission (1). It is characterized by fluctuating weakness and fatigue of the striated musculature while preserving smooth musculature. The disease is rare, with an estimated pooled incidence rate of 5.3 cases per million persons per year, and can occur at any age, in both sexes (2). However, it is twice as common in females, with a peak incidence between the third and fourth decades of life, which coincides with the reproductive period of a woman, which requires special clinical and therapeutic caution.

A review of the existing literature indicates the complexity of the relationship between MG and pregnancy, in terms of the existence of a two-way relationship: pregnancy can affect the course of the disease, but MG can affect childbirth and the occurrence of postnatal complications (3). However, a review of the existing literature has limited extrapolation in current clinical practice (4). Previous studies have been mostly retrospective or individual case reports. The studies differed significantly in the data provided on clinical status before and during pregnancy, disease course, therapy, obstetric interventions, and pregnancy outcome. Many were difficult to evaluate due to sparse details. There was broad agreement on certain points with marked differences in others. In general, what can be concluded is that the course of MG during pregnancy as well as the course and outcome of pregnancy are very variable and difficult to predict.

This study intended to contribute to the further elucidation of the relationship between MG and pregnancy, a thorough evaluation of the clinical course, delivery, and neonatal outcome of pregnant women with the diagnosis of myasthenia gravis,

followed in University Clinical Center Niš which attracts a large number of patients from south-eastern Serbia.

Materials and methods

The study included 15 pregnant women with MG in whom 25 pregnancies were recorded, followed at the University Clinical Center Niš (UCC Niš) in the period 2003-2020. A prospective study was conducted on 7 women (10 pregnancies). In 8 women (15 pregnancies), the required data were obtained by retrospective analysis of medical records. Out of a total of 15 pregnant women, 13 women suffered from acquired MG, and two from juvenile MG. The clinical course of the disease during pregnancy, labor, and postpartum period was reviewed, as well as the neonatal period in the 23 infants born to MG mothers. The condition for this study was that the diagnosis of MG was made before pregnancy. The stage of the disease was determined according to Osserman's classification.

Descriptive variables included: Total number of pregnancies, the average age at the time of pregnancy, the average duration of the disease until pregnancy, outcome (delivery on time, spontaneous abortion, vaginal delivery), obstetric interventions (Caesarean section, Vacuum extractor), the course of MG during pregnancy and puerperium (exacerbation of the disease), neonatal complications (transient neonatal myasthenia gravis (TNMG)).

Clinical variables included clinical characteristics of pregnant women with MG before conception: age at the time of diagnoses (Dg), Osserman classification, anti nAChR antibodies, thymectomy, pharmacological therapy, pharmacological remission, complete remission.

The criteria for improvement, unchanged or worsening of MG during pregnancy were the following:

1) Improvement: patients who had clinical improvement of the symptoms and decrease of the dosage of the medications,

2) No change: patients with no clinical change in their symptoms and same doses of medications compared with before pregnancy.

3) Deterioration: patients who had a deterioration of the disease (worsening of the Osserman's stage) and an increase in the dosages of medications compared with before the pregnancy, or the need for immunosuppressant drugs such as azathioprine and/or prednisone.

Transient neonatal myasthenia gravis was diagnosed based on clinical signs of generalized hypotonia, sucking disturbances, a weak cry, and respiratory difficulties.

Results

The study included 15 patients with MG, mean age 21.13 ± 7.25, in whom 25 pregnancies were observed. The presence of anti nAChR antibodies was confirmed in 13 patients. No antibodies were tested in two patients. Nine patients underwent thymectomy in the same year as Dg, except for one patient where thymectomy was performed after pregnancy. In 9 pregnant women, pharmacological remission was achieved before conception, three pregnant women were in complete remission (without therapy), while three pregnant women had symptoms of the disease before pregnancy. Three patients had three pregnancies each, two of which were twin sisters who got sick from MG at the age of six. Four patients had 2 pregnancies each, while the remaining eight patients had 1 pregnancy each.

The mean age of women at the time of pregnancy was 28 ± 5.5 years (Table 2). The average duration of the disease until pregnancy was 7.7 ± 7.68 years, or 3.58 ± 1.35 years if we exclude two twins with juvenile MG.

Spontaneous abortion was observed in two pregnant women (8%) in the second month of pregnancy (Table 2). The first patient was in complete remission and had three pregnancies. Spontaneous abortion occurred in the second pregnancy with transient exacerbation of the disease. Her previous and next pregnancy passed without any complications, with a vaginal delivery on time. In the second case, it was a patient with juvenile MG who also had three pregnancies, and who was in complete remission before conception. During the first two pregnancies, there was an exacerbation of the disease, but the course of pregnancy and childbirth passed without complications, while the second pregnancy ended in a miscarriage in the second lunar month.

In the remaining cases (92%), childbirth was completed on time (Table 2). Twelve women (52%) gave birth vaginally. In two cases, a vacuum extractor was used (8.7% of the total number of births, and 16.6% of all vaginal births).

One newborn was diagnosed with TNM. There were no stillbirths or physical anomalies. Clinical worsening was recorded during 10 pregnancies (40%), in 8 pregnant women (Table 1, Figure 1, Figure 2).

The largest number of relapses was recorded in the first trimester of pregnancy, but it was also recorded in the last 2 weeks of pregnancy (4%), as well as postpartum (12%). It is important to emphasize that of the total number of pregnancies with MG, one clinical deterioration occurred after a miscarriage in the second month of pregnancy. In most cases (52%), the situation was unchanged. Improvement was recorded in 2 pregnant women in the third trimester (8%).

Table 1. Clinical characteristics of pregnant women with MG before conception

Pregnant women	Age at the time of Dg (years)	Osserman	Anti nAChR antibodies	Thymectomy	Therapy	Remission pharmacol.	Remission complete	Number of pregnancies
1*	18	IIa	/	+		-	+	3
2	17	IIb	/	+		-	+	1
3	24	IIa	+	+		-	+	1
4*	25	IIa	+	+	+	+	-	1
5*	33	IIb	+	+	+	+	-	1
6	25	IIa	+	-	+	-	-	2
7*	6	IIa	+	-	+	+	-	3
8*	6	IIa	+	-	+	+	-	3
9	23	I	+	-	+	+	-	1
10	23	IIa	+	-	+	+	-	1
11*	24	IIa	+	+	+	+	-	2
12	25	IIb	+	+	+	+	-	2
13	24	IIb	+	+	+	-	-	1
14*	26	IIb	+	- (Post partum+)	+	-	-	1
15*	18	IIb	+	+	+	+	-	2

*exacerbation of the disease

Table 2. Characteristics of pregnancy and childbirth

Characteristics	No/years	(%)
Total number of pregnancies	25	
The average age of women at the time of diagnoses	21.13 ± 7.25	
The average age at the time of pregnancy	28 ± 5.5	
The average duration of the disease until pregnancy	3.58 ± 1.35 7.7 ± 7.68*	
Delivery on time	23	92%
Spontaneous abortion	2	8%
Vaginal delivery	12	52%
Caesarean section	11	48%
Vacuum extractor	2	8.7%
Exacerbation of the disease	10	40%
TNMG	1	4.35

* pregnant women with juvenile myasthenia gravis included;
TNMG-transitory neonatal myasthenia gravis

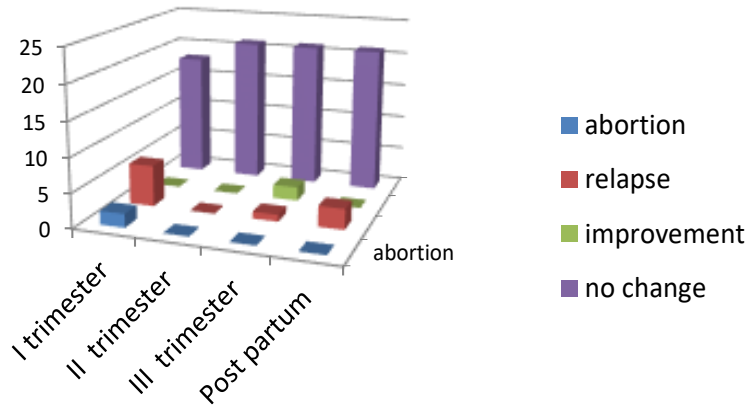

Figure 1. The course of the myasthenia gravis during pregnancy and postpartum

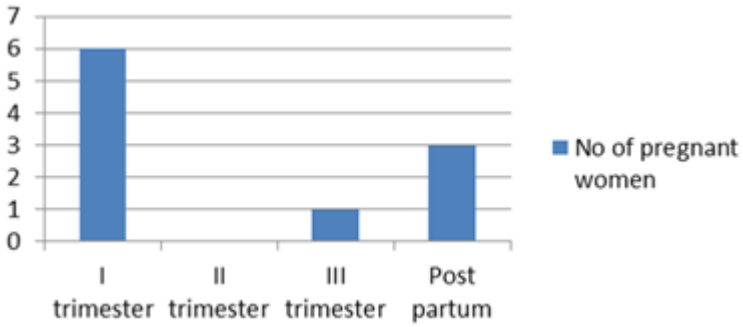

Figure 2. Deterioration of myasthenia gravis symptoms during pregnancy and post partum

Discussion

Due to the high prevalence of MG in women of reproductive age, pregnancy in patients with MG is not uncommon, which requires special clinical and therapeutic caution. In general, the analysis of the outcome of chronic and rare diseases with unpredictable and fluctuating courses is difficult. The clinical course of MG in pregnancy is variable and unpredictable (5-7). Exacerbations, myasthenic crises, but also remissions of the disease are possible. The data in our study show that 10 pregnancies out of a total of 25, were accompanied by a worsening of the clinical course of MG, which means that in our group of patients the percentage of relapses was high (40%). These data coincide with the results of Plush from 1991, where the relapse rate was 41% of a total of 322 pregnancies followed by 225 women with MG (8). However, in other studies, a lower percentage of relapses was noted. For example, in a study conducted by Batocchi et al., clinical worsening of MG was registered during 10 pregnancies (19%), out of a total of 54 (9). Djelmis et al. recorded an even lower relapse rate - 14.5% of a total of 69 pregnancies followed in 65 patients with MG (10). In the remaining pregnant women in our study, the largest number (52%) had an unchanged clinical picture of MG, while in two pregnant women (8%) there was a clinical improvement in the third trimester of pregnancy.

The results of previous researches show that the first trimester and postpartum period appear to be the most critical periods for MG exacerbation, which is associated with reduced progesterone secretion in that period. By that, in our study, the highest percentage of exacerbations was recorded in the first trimester of pregnancy (24%) (11, 12). Worsening in the puerperium was observed in three pregnant women, in three pregnancies (12%), which is a significantly lower percentage compared to other studies. A study by Batocchi et al. recorded postpartum worsening of disease symptoms in 28% of cases. In his study, Hoff recorded a percentage of disease exacerbations in the postpartum period of 29.8% (11). In a study by Djelmis et al., this percentage is slight - 16% (10). Although the critical

period for relapses is the first trimester, worsening of the clinical course is possible even later. In our study, one pregnant woman (4%) showed a slight emphasis on general weakness and fatigue at the end of the third trimester.

The two patients in our study were twin sisters who developed MG at the age of six. The patients achieved complete remission during life. Both patients had three pregnancies each. In all pregnancies, the disease was exacerbated in the first trimester. In one patient, the third pregnancy ended in a miscarriage in the second month of pregnancy. Three patients with MG had two pregnancies each. In one patient, both pregnancies passed without complications. Another patient had a clinical worsening in the second pregnancy. The third patient relapsed in the first pregnancy, while the second pregnancy passed without complications. These results support previous observations that there is no correlation between the clinical course before pregnancy and during pregnancy, as well as that based on the clinical course in one pregnancy, it is not possible to predict the course of subsequent pregnancies. Also, pregnancy did not adversely affect the long-term clinical course of MG in our patients, which is by the data from the literature.

There is not much data in the literature on the influence of thymectomy on the clinical course of MG during pregnancy and after childbirth, as well as on the occurrence of neonatal MG, and these data are contradictory. Although published case reports suggest that the incidence of clinical deterioration is higher in patients who have not been thymectomized, Roth et al. could not confirm this in their study (13). The clinical course of MG was unpredictable during pregnancy and in the postpartum period in both thymectomized and non-thymectomized patients. Thymectomy did not have a significant effect on the course of MG. However, it was observed that women who underwent thymectomy before pregnancy were in better general condition even in the case of disease exacerbation. Our data is consistent with the data of Roth and associates. In our group of patients, there was no significant difference in the occurrence of relapse in thymectomy and non-thymectomy women before conception. Also, the time interval between thymectomy and pregnancy did not affect the occurrence of relapse.

In addition to exacerbations of the course of the disease, other potential complications such as miscarriages or premature births have been described in pregnant women with MG. Spontaneous abortion may occur with a slightly increased frequency in MG (14, 15). In the Batocchi et al. study, 10 pregnancies (15.6%), resulted in abortion (9). In a French study 19.4% of pregnancies were found, 14.8% in a Turkish cohort, 14.3% (16) in Brazil (17). This indicates a rate of around 15%. This is similar to the miscarriage rate in the general population of 10-20% among women who know they are pregnant. In our study, spontaneous abortion was observed in two pregnancies (8%), in two different pregnant women, in both cases in the second month of pregnancy. Both patients had three pregnancies each. In the first patient, the first and third pregnancies ended on time, without complications, while the second pregnancy resulted in a miscarriage and exacerbation of the disease afterward. In the second pregnant woman, the first two pregnancies ended in the term, while the third resulted in a miscarriage. In all other cases, childbirth occurred on time.

In a large retrospective study, Hoff et al. concluded that interventions during childbirth were more frequent in the group of patients with MG than in the reference group and that the percentage of cesarean section was statistically significantly higher than in the reference group (17.3% vs. 8.6 %) (13). The results of Italian authors indicate a higher rate of cesarean section in pregnant women with MG compared to the reference group, but this difference is not statistically significant (30% vs. 14%) (9). In our study, the percentage of cesarean section was 34%, which is a higher percentage compared to the results of Hoff and co-workers, as well as compared to the average rate of cesarean section in Europe (elective cesarean section as elective intervention - 10.7% and 25.2% total number of cesarean section), although large variations have been observed among European countries (18). The disadvantage of our study is the lack of data on the average rate of cesarean section in Serbia.

Neonatal complications in pregnant women with MG include TNMG, as well as congenital anomalies. In general, TNM is a complication that affects around 10% of children born to mothers who have MG but can reach up to 30% (8, 10). This is due to antibodies against AchR or MuSK that are transported from the mother's circulation, across the placenta, and to the fetus (19). No correlation was observed between the severity of the mother's clinical picture in pregnancy and the occurrence of neonatal MG, and similar results were obtained in a study in Italy. Transient neonatal MG was registered in only one of a total of 23 newborns (4.3%) in our study. No thymectomy was performed on the mother of this newborn. These results coincide with the results of a study by Roth et al. where only 2 (16.7%) of the 12 newborns alive showed myasthenic symptoms. Both newborns belonged to the group of non-thymectomized mothers, which denote a possible positive effect of thymectomy. However, previous research has not yet confirmed with certainty the positive benefit in newborns whose mothers were thymectomized before pregnancy. (16, 17). No congenital anomalies were identified in any of the newborns.

Conclusion

The clinical course of MG in pregnancy is variable and unpredictable, but pregnancy does not affect the long-term course of MG. On the other hand, pregnancy in the large majority of MG women is without complications. Spontaneous abortion may occur with a slightly increased frequency in MG. Patients with MG have an increased rate of Cesarean section, mostly as a precaution to avoid exhaustion, which is often unnecessary. Neonatal complications in pregnant women with MG include TNMG. Thymectomy in mothers with MG before pregnancy is not a guarantee for a stable clinical course of MG during pregnancy but could potentially have a po-

sitive benefit for the newborn. To reduce the risk of complications, good cooperation between neurologists, gynecologists, and neonatologists is necessary during pregnancy and childbirth. MG is not a reason to give up motherhood and MG patients should be supported in their desire to conceive.

Acknowledgement

The authors would like to thank the ministry of Education, Science and Technological Development of Republic Serbia (Grant No 451-03-68/2022-147200113).

References

1. Newsom-Davis J. The emerging diversity of neuromuscular junction disorders. Acta Myol 2007; 26(1): 5-10. [PubMed]
2. Carr A, Cardwell C, McCarron P, McConville J. A systematic review of population based epidemiological studies in Myasthenia Gravis. BMC Neurology 2010; 10:46. [CrossRef] [PubMed]
3. Midelfart-Hoff J, Kjersti-Daltveit A, Gilhus NE. Myasthenia gravis-Conseqences for pregnancy, delivery, and the newborn. Neurology 2003;61:1362-6. [CrossRef] [PubMed]
4. Norwood F, Dhanjal M, James N, Jungbluth H, Kyle P, et al. Myasthenia in pregnancy: best practice guidelines from a UK multispecialty working group. J Neurol Neurosurg Psychiatry 2013;00:1-6. [CrossRef] [PubMed]
5. Plauche WC. Myasthenia gravis. Clin Obset Gynecol 1983;26:592-604. [CrossRef] [PubMed]
6. Rosenbaum RB, Donaldson J. Peripheral nerve and neuromuscular disorders. Neurol Clin 1994;12:471-3. [CrossRef] [PubMed]
7. Eymard B, Morel E, Dulac O, Moutard-Codou ML, Jeannot E, Harpey JP, et al. Myasthenia and pregnancy: a clinical and immunologic study of 42 cases (21 neonatal myasthenia cases. Rev Neurol (Paris) 1989;145:696-701. [PubMed]
8. Gilhus NE. Myasthenia Gravis Can Have Consequences for Pregnancy and the Developing Child. Front Neurol 2020. [CrossRef] [PubMed]
9. Batocchi AP, Majolini L, Evoli A, Lino MM, Minisci C, Tonali P. Course and treatment of myasthenia gravis during pregnancy. Neurology 1999;52:447-52. [CrossRef] [PubMed]
10. Djelmis J, Sostarko M, Mayer D, Ivanisevic M. Myasthenia gravis in pregnancy: report on 69 cases. Eur J Obstet Gynecol Reprod Biol 2002;104:21-5. [CrossRef] [PubMed]
11. Hoff JM, Daltveit AK, Gilhus NE. Myasthenia gravis: consequences for pregnancy, delivery, and the newborn. Neurology 2003;61:1362-6. [CrossRef] [PubMed]
12. Batocchi AP. Pregnancy and myasthenia gravis. In: Vincent A, Martino G. Autoantibodies in neurological diseases. Milan: Springer-Verlag Italia, 2002;28-39. [CrossRef]
13. Roth TC, Raths J, Carboni G, Rösler K, Schmid RA. Effect of pregnancy and birth on the course of myasthenia gravis before or after transsternal radical thymectomy. Journal of Cardio-thoracic Surgery 2006; 29:231-5. [CrossRef] [PubMed]
14. Ramirez C, de Seze J, Delrieu O, Stojkovic T, Delalande S, Fourrier F, et al. Myasthenia gravis and pregnancy: clinical course and management of delivery and the postpartum phase. Revue Neurologique 2006;162:330-8. [CrossRef]
15. Tanacan A, Fadiloglu E, Ozten G, Gunes AC, Orgul G, Beksac MS. Myasthenia gravis and pregnancy: retrospective evaluation of 27 pregnancies in a tertiary center and comparison with previous studies. Irish J Med Sci 2019;188:1261-7. [CrossRef] [PubMed]
16. Ducci RD, Lorenzoni PJ, Kay CSK, Werneck LC, Scola RH. Clinical follow-up of pregnancy in myasthenia gravis patients. Neuromusc Disord 2017;27:352-7. [CrossRef] [PubMed]
17. Macfarlane AJ, Blondel B, Mohangoo AD, Cuttini M, Nijhuis J, Novak Z, et al. Wide differences in mode of delivery within Europe: risk-stratified analyses of aggregated routine data from the Euro-Peristat study. BJOG 2016;123(4):559-68. [CrossRef] [PubMed]
18. Gilhus NE HY. Maternal myasthenia gravis represents a risk for the child through autoantibody transfer, immunosuppressive therapy and genetic influence. Eur J Neurol 2018;2018:1-8. [CrossRef] [PubMed]
19. Eden RD, Gall SA. Myasthenia gravis and pregnancy: a reappraisal of thymectomy. Obstet Gynecol 1983; 62(3):328-33. [CrossRef] [PubMed]

Originalni rad **UDC: 616.8 009.1:618.2**
doi:10.5633/amm.2022.0303

STUDIJA DVOSMERNE POVEZANOSTI MIASTENIJE GRAVIS I TRUDNOĆE

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Usled velike prevalencije miastenije gravis (MG) kod žena u reproduktivnom periodu, pojava trudnoće kod ovih bolesnica nije neuobičajena. Ovo zahteva poseban klinički i terapijski oprez. Postoji dvosmerni odnos MG i trudnoće: trudnoća može uticati na klinički tok MG, a takođe sama bolest može uticati na porođaj i pojavu postnatalnih komplikacija. Cilj naše studije bio je da se proceni uticaj MG na klinički tok, porođaj i ishod neonatusa kod trudnica. Klinička slika tokom trudnoće, porođaja i u postpartalnom periodu praćena je kod 23 novorođenčeta, rođenih od strane 15 majki sa dijagnozom MG. Spontani abortus primećen je u dva slučaja (8%), u drugom mesecu trudnoće. Kod jednog novorođenčeta dijagnostikovana je tranzitorna neonatalna MG. Nije bilo mrtvorođenih i nije bilo fizičkih anomalija kod novorođenčadi. Kliničko pogoršanje utvrđeno je tokom 10 trudnoća (40%) kod 8 trudnica. Klinički tok MG tokom trudnoće je varijabilan i nepredvidljiv, ali trudnoća ne utiče na dugotrajni ishod MG. Spontani abortus je potencijalna komplikacija kod žena sa MG. Carski rez je intervencija koja se češće sprovodi kod žena sa MG u odnosu na opštu populaciju. Timektomija kod žena sa MG, pre porođaja, može imati pozitivni efekat na novorođenčad. Neonatalna tranzitona MG bila je retka u našoj populaciji. Nije bilo kongenitalnih anomalija kod 23 novorođenčeta u našoj ustanovi.

Acta Medica Medianae 2022;61(3):20-26.

Ključne reči: *miastenija gravis, trudnoća, klinički tok*