

Effect of pregnancy and birth on the course of myasthenia gravis before or after transsternal radical thymectomy[☆]

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Abstract

Objective: Myasthenia gravis (MG) affects women at childbearing age. Therefore, the question arises if these patients should become pregnant and if thymectomy has a positive effect on the course of MG in pregnant patients. **Methods:** Fifteen pregnancies had been followed retrospectively. All patients underwent transsternal radical thymectomy for MG. The course of MG in the period before, during, and after the pregnancy was scored according to Ossermann's classification. The effect of thymectomy on delivery and on the newborns was evaluated. **Results:** Patients were divided in two groups: pregnancies before (group I, $n = 8$) and after (group II, $n = 7$) thymectomy. During pregnancy, in group I, one deterioration was observed and in seven patients the disease was unchanged. In group II, one deterioration, five unchanged courses, and one improvement were observed. In the postpartum period, in group I, seven patients did not change and one improved. In group II, two deteriorations, three unchanged courses, and two improvements were observed. Before pregnancy, group II patients were in a better Ossermann stage in comparison with those in group I. Eight of the 12 deliveries were spontaneous (three abortus). Myasthenic symptoms were observed in two newborns in group I. **Conclusion:** Our data suggest that MG is not prohibitive to have children. The course of MG after transsternal radical thymectomy is often ameliorated. A better MG-stage, reached after thymectomy, before pregnancy seems to be correlated with a better course during pregnancy.

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1. Introduction

Myasthenia gravis (MG) is an acquired chronic autoimmune disease affecting the motor endplates of the voluntary muscles. It is characterized by excessive fatigue and weakness of the striated muscle system. Non-striated muscles including uterus are not affected. The prevalence of MG is 14.1 patients per 100,000 (17.1 for women and 10.8 for men) without any ethnic, occupational, or endemic area predilection, but although it affects both sexes, it has a predilection for young females (with mean age of onset at 34.9 years) [1].

The most common symptoms at the onset of MG are ptosis and diplopia, which occur in 65% of all patients, but only 10% remain confined to the extrinsic ocular muscles [2]. In most cases, the disease spreads gradually to the skeletal muscles

causing weakness of the proximal limb girdle and the bulbar muscles with dysarthria, dysphagia, and poor mastication. Generalized weakness and involvement of respiratory muscles represent the final stage, which may lead to death in more than 29% of untreated patients [2].

The course of MG is characterized by unpredictable remissions and exacerbations. Exacerbations of MG are often associated with physical or emotional stress. This may be observed during pregnancy and the postpartum period.

The underlying autoimmune mechanism of MG is the production of specific IgG antibodies directed against the acetylcholine receptor (AChR) of the motor-endplate with functional impairment. The initial cause of antibody formation is unknown, but the thymus, as the site of T-lymphocyte education with resulting self-tolerance, is thought to be an integral part in the pathogenesis of MG.

Thymectomy has been used to remove the main source of antibody production since the first operation for MG by Sauerbruch in 1911 [3]. Today, transsternal radical thymectomy is an effective part of the treatment of MG, as in long-term evaluation more than half of the patients show objective clinical improvement, with more than one quarter

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of complete remission. Two-third of patients lead a normal life with normal everyday activity including regular sports [4].

The purpose of the present study was to evaluate the effect of pregnancy and birth on the course of MG symptoms and, most importantly, to compare the course of pregnancies and deliveries before and after transsternal radical thymectomy. In addition, the effect of thymectomy on the development of the newborn was evaluated.

2. Patients and methods

Six women underwent transsternal radical thymectomy for MG between 1986 and 1989 either before or after their pregnancies.

The diagnosis of MG was confirmed by a neurologist's clinical assessment, electromyographic studies, edrophonium chloride (Tensilon) test, and circulating acetylcholine receptor antibodies.

Indications for surgery included new onset of generalized MG and failure of long-term conservative therapy. The operative technique was median sternotomy, followed by opening the pleural space and exploration of the mediastinum up to the cervical thymic extension and laterally down to the phrenic nerves. All thymic tissues and the entire pericardial fat and mediastinal fat from the diaphragm to the thyroid were removed en bloc.

Six women of our patients had 15 pregnancies ($n = 15$), eight before (group I) and seven after (group II) thymectomy. All six women had all their pregnancies either before or after the thymectomy.

The courses of MG-symptoms in the period before, during, and after their pregnancies were evaluated by telephone interviews and detailed written questionnaires until November 2002.

Data were collected in both groups on specific topics such as changes of MG-symptoms with the menstruation cycle or oral contraceptives, number and duration of pregnancies and number of abortions or premature births, as well as intensity and changes of MG-symptoms (both objectively, according to the classification of Ossermann, and subjectively), myasthenic crises, medications, or plasmaphereses needed in the period before, during, and after pregnancy and birth. Furthermore, the way, the duration and complication of delivery, myasthenic symptoms of the newborn in the postpartal period, breast-feeding, as well as inter-current disease independent of MG during all these periods were assessed.

Patients without symptoms or medication for MG were considered to be in "complete remission." "Improvement" was defined as lower stage and "deterioration" as higher stage according to the classification of Ossermann (Table 1) in comparison with the previous stage. Besides the Ossermann's classification, the subjective changes of symptoms, particularly in intensity, which added no other symptoms to change the Ossermann stage, have also been determined.

The study compared the stage of MG, before, during, and after pregnancy, in order to compare the two groups, before and after thymectomy. We also evaluated the complication rate of the delivery and the newborn with MG symptoms between groups.

Table 1
Classification of the MG symptoms according to the Ossermann's scale

Classification of Ossermann	
I	Ocular myasthenia characterized by ptosis and diplopia.
IIa	Slow onset, frequently ocular, gradually spreading to the skeletal musculature.
IIb	Gradual onset with dysarthria, dysphagia, and poor mastication.
III	Rapid onset of severe bulbar and skeletal muscle weakness with involvement of the respiratory muscles.
IV	Severe myasthenia gravis developing at least 2 years after onset.

3. Results

At the time of the assessment, the mean age of the six women was 42.6 years (range 32.7–55.6). Mean duration of MG-symptoms was 23.2 years (range 15.4–35.8), mean time after diagnosis of MG was 16.3 years (range 13.4–19.8) and mean time after thymectomy was 14.6 years (range 13.3–16.6). Mean time after delivery was 15.9 years (range 0.08–32).

Only one patient ever remarked some changes of MG-symptoms along with the menstruation cycle, and among the four patients who had ever taken some oral contraceptives, no patient ever remarked any changes of MG-symptoms due to this medication.

No mortality occurred. None experienced a myasthenic crisis, nor required treatment with plasmapheresis.

All patients breast-fed their babies for up to 11 months without problems.

The clinical course of all patients is summarized in Fig. 1. *Pregnancies before thymectomy (group I, $n = 8$):* During pregnancy, none of the patients improved, seven (87.5%) showed no change, and one (12.5%) deteriorated by one grade in terms of the Ossermann classification in comparison to the value prior to the pregnancy.

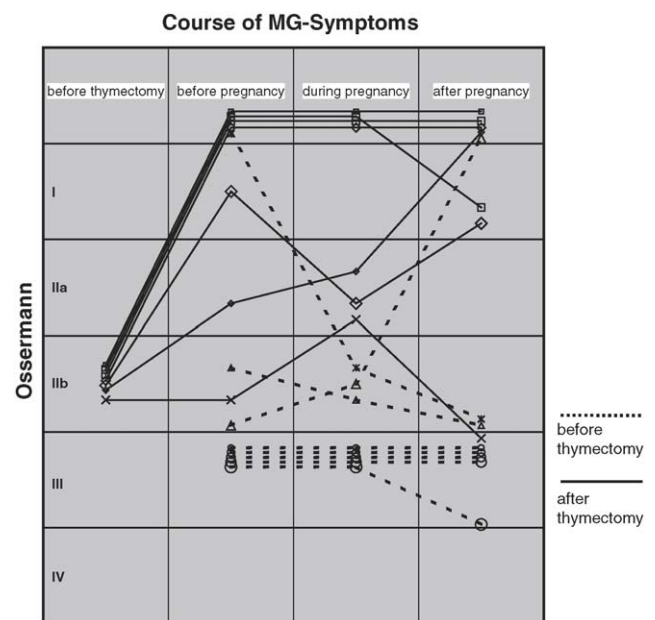


Fig. 1. Evolution of the course of MG—Ossermann stage of the 15 pregnancies before (interruption line) or after (continuous line) thymectomy, in the period before-, during- and after pregnancy.

In the postpartal period, one (12.5%) improved by one grade, and seven (87.5%) showed no change in comparison to the period of pregnancy.

While pregnant, one patient (12.5%) showed subjective improvement, five (62.5%) showed no change, and two (25%) reported subjective deterioration of MG-symptoms.

In the postpartal period, subjectively, one (12.5%) showed improvement, four (50%) showed no change, and three (37.5%) a slight deterioration of MG-symptoms.

Three (37.5%) deliveries were spontaneous, two (25%) were complicated by insufficient uterine contractions and therefore needed external support such as vacuum extraction and manual abdominal pressure maneuvers, respectively, and three (37.5%) were missed abortions (at 11, 12, and 17 weeks gestation), which could not clearly be attributed to MG. No caesarean section was needed. Mean duration of birth was 5 h (range 20 min to 12 h).

In the postpartal period, two (40%) of the five newborns ($n = 5$) in this group showed myasthenic symptoms such as weak cry, problems in drinking or general weakness up to 6 weeks after labor.

In this group, no medical treatment of MG was necessary during pregnancy.

Pregnancies after thymectomy (group II, $n = 7$): During pregnancy, one patient (14.3%) improved by one grade of the Ossermann classification, five (71.4%) showed no change, and one (14.3%) a deterioration of one grade in comparison to the stage.

In the postpartal period, one patient (14.3%) improved by one grade and one (14.3%) by two grades of Ossermann classification; three (42.9%) showed no change, and two (28.6%) a clinical deterioration of one grade in comparison to during pregnancy.

Subjectively, during pregnancy, two (28.6%) showed slight improvement, four (57.1%) no change, and one (14.3%) deterioration.

In the postpartal period, two patients (28.6%) showed subjective improvement, three (42.9%) no change, and two (28.6%) deterioration (the subjective changes correspond exactly with the objective ones).

Five (71.4%) deliveries were spontaneous; one (14.3%) was complicated by insufficient uterine contraction and therefore needed vacuum extraction, and one (14.3%) was a caesarean section by absence of labor's progression with fetal suffering signs in cardiotocogram. No missed abortion was reported. Mean duration of birth was 12.8 h (range 3.5–36).

None (0%) of the seven newborns suffered from myasthenic symptoms.

Two patients (28.6%) needed medical treatment for MG with prostigmine (one with 10–30 mg/day and one with 180–240 mg/day) during pregnancy.

4. Discussion

The influence of pregnancy on autoimmune disorders has been of interest because of the tolerance of the immune system in this particular period.

On the other hand, the effect of MG on pregnancy and delivery, with or without thymectomy, is poorly studied.

Thymectomy has been considered by many authors as the treatment of choice for MG [4–8] and a positive effect has been repeatedly demonstrated since the initial report by Blalock et al. [9] in 1939. The beneficial effect of thymectomy on MG is, therefore, generally accepted and can also be confirmed with the present study. However, the role of the thymus and the etiology of this disorder have yet been fully elucidated.

For young women, the effect of the different treatment modalities, especially of thymectomy, on the course of a pregnancy is of great interest.

Obviously, analysis of the outcome of chronic and rare diseases with unpredictable and fluctuating course is difficult. In addition, a number of different classifications for MG are used throughout the literature: Ossermann, Ossermann modified, Oosterhuis, Myasthenia Gravis Foundation of America, Besinger score, de Filippini, all of which try to integrate the neurologist's assessment and the patient's perception of disease-related symptoms and their limitations. Therefore, it is difficult to assign the various descriptions of symptoms of our patients to one objective classification because none of them integrates the numerous subjective variations of MG-manifestations described by the patients. According to our previous studies [4,5], the classification of Ossermann was used. In addition, we tried to consider subjective changes which on one hand did not make any difference according to the objective classification, but on the other hand were significant regarding the subjective perception of the disease.

There are a number of publications on the changes of MG-symptoms during pregnancy. In the present study, however, we focused on the effect of thymectomy on the course of MG-symptoms during pregnancy, birth, and the postpartum period. The main interest was to ascertain if thymectomy could have a possible positive effect on the symptoms of MG regarding pregnancy, and therefore, if thymectomy should particularly be recommended to young women with MG who are planning to have children.

We observed that each pregnancy, included these of the same mother, had a singular pattern, which was not necessarily similar to the course of the previous pregnancy.

Our present study confirms that the terms "variable" and "unpredictable" can be applied to the course of MG including the period during pregnancy and also conversely on the effect of pregnancy on MG. As 1899, Sinkler [10] reports that a woman with MG improved during her sixth month of gestation, but symptoms reappeared after delivery. Many subsequent series have confirmed that approximately two thirds of gravid myasthenic women either remain the same or improve the symptoms of MG during their pregnancy, while one third have an exacerbation of symptoms. Viets et al. [11] in their review of the literature and presentation of 8 patients with 11 pregnancies, state unequivocally that the course of MG in most cases is profoundly affected by pregnancy. All their patients showed some change during pregnancy with most patients experiencing remissions. In four of their patients, there were no relapses in pregnancy. The other four had both relapses and remissions with the relapse occurring in the first trimester and subsequent remission. Ossermann and Kaplan [12] reported 25 patients with 36 pregnancies. In these patients, 33% had relapses with

no change in their disease pattern and 44% reported a remission of their myasthenic symptoms during pregnancy. Plauche [13] in his review of the English literature from 1938 to 1964 appraises 97 patients with 126 pregnancies. In this report, 57% of all patients exhibited exacerbation at some time during pregnancy, 46% had no change in symptoms, and 38% had remissions during the same period. He concluded that there is no real difference between the number of patients showing relapses or remissions in comparison with the antepartum period. In his update from 1979 [14], he noted that equal proportions of non-thymectomized patients exhibit exacerbations, remissions, and no change in clinical symptomatology. In the literature review of 322 pregnancies from 1991 [15], he reported that 32% of the pregnancies caused no change in the status of MG through gestation and the postpartum period, 28.6% had at least partial remission, and exacerbation occurred during gestation in 41% and in 29.8% in the puerperium. Reports of further investigators confirmed the unpredictable nature of MG in pregnancy [16,17], and so do our own results: most of the spontaneous course of pregnancies (of non-thymectomized patients) showed no change of MG-symptoms during gravidity and the postpartum period (87.5%), but one (14.2%) exacerbated during pregnancy and one (14.2%) improved in the postpartum period.

Thus, the hypothesis of an increased tolerance of the immune system during pregnancy with the spontaneous expected positive effect of MG is not clearly demonstrated.

A majority of the previous publications described worsening of MG symptoms immediately after delivery, explained either by the reactivation of the body's immunological response [18] or by puerperal infections such as endometritis, pyelonephritis, or cystitis [19], but in our experience we cannot confirm these observations.

Reports on the effects of thymectomy on the course of MG-symptoms regarding to gestation and postpartum period are much less often found in literature. Ip et al. [20] reported for the first time, a thymectomy for treatment of a myasthenic crisis during pregnancy. There are contradicting reports regarding the number and severity of exacerbations in pregnancy in patients who have had a thymectomy and in those who have not undergone the procedure. In the case reported by Eden and Gall [21] from 1983, a significant improvement of the clinical course following thymectomy during subsequent pregnancy could not be demonstrated. A review of previous case reports [11,13,14,16,22,23], however, suggests that although the incidence of remission in the thymectomy group is lower than that of the non-thymectomy group, the incidence of clinical exacerbation appears to be greater in the non-thymectomy group. Clinical exacerbation occurred in 60% of pregnancies in the non-thymectomy group as compared to 30% in the thymectomy group [21]. Unfortunately, our data could not confirm these trends: The course of MG-symptoms of thymectomized as well as non-thymectomized patients seems to be unpredictable during both, pregnancy and postpartum period. Severe exacerbations in pregnancies may occur after thymectomy as well as there may be an enormous improvement in pregnancies before thymectomy. Therefore, thymectomy seems to have no remarkable effect on the course of the myasthenic

symptoms, however, there are benefits regarding a pregnancy: Women who underwent thymectomy before getting pregnant are in a better general condition and MG-status. Consequently, if these women become pregnant, they are able to support and manage a possible deterioration much better than a non-thymectomized women. Even thymectomized women experience severe exacerbations, they are still in a better state than non-thymectomized women without exacerbation.

The question, if the newborn could profit of this positive effect of the thymectomy of his mother, is not yet fully clarified. In retrospective reviews of pregnant females with and without thymectomy, there was no difference in the development of neonatal MG between thymectomized and non-thymectomized pregnant women [21,24]. Classically, transitory neonatal myasthenia is a complication affecting 10–20% of children born by mothers who have MG [15], but may reach up to 30% [19]. Symptoms usually occur several hours or days following delivery and have a mean duration of 3 weeks, but may persist up to 3 months. The symptoms are caused by transplacental transfer of acetylcholine receptor antibodies, but there is no correlation between the severity of maternal disease or the level of acetylcholine receptor antibody titers and the occurrence of neonatal MG [18,15,25].

In the present study, only 2 (16.7%) of the 12 newborns alive showed myasthenic symptoms. Both newborns belonged to the group of non-thymectomized mothers. The rate of neonatal MG was zero in children of thymectomized mothers, in comparison to 40% in children of non-thymectomized mothers, which denote another possible positive effect of thymectomy.

The development of the newborn seems to be completely independent of the presence or absence of the thymic gland by the myasthenic mother [21]. Also, in our study, there are neither alterations in length and weight of newborns of non-thymectomized mothers, nor any remarkable effects on the duration of labor until delivery of thymectomized mothers. In our series, only one caesarean section (6.6%) was performed, but a rate up to 17.4% is reported in the literature [19]. Likewise, no difference between the two groups was observed regarding premature birth, which was reported to occur between 13% and 66% in non-thymectomized patients [15,21,25]. We also did not observe associated congenital anomalies which have been rarely reported [25].

5. Conclusions

The data show that transsternal radical thymectomy improves MG-stage, which is correlated with a better course of MG during pregnancy and the postpartum period, as in most cases the absence of changes of MG-symptoms during the gravidity and puerperium has been observed.

Importantly, no myasthenic symptoms in the newborn after transsternal radical thymectomy of the mother have been observed.

Because MG is classically affecting women at the child-bearing age, we concluded that thymectomy could be legitimately recommended in this subgroup of patients,

however, a good strong collaboration between the different specialists to monitor the evolution of the pregnancy and delivery is needed.

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