Myasthenia gravis in pregnancy: report on 69 cases
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Abstract

Objective: To review our experience with pregnancies in women with myasthenia gravis (MG). Study design: Sixty nine pregnancies among 65 women with MG patients managed by our department over 28 years were included. The course of the disease in pregnancy, mode of delivery and postpartal period were evaluated. Results: One pregnancy miscarried. In 15% of patients the MG deteriorated in pregnancy a further 16% in the puerperium. 17% of pregnancies were delivered by cesarean section, one due to myasthenia exacerbation. All women with puerperal infections developed exacerbations. One neonatal death, not attributable to myasthenia, was recorded. Transitory neonatal myasthenia gravis (TNMG) was diagnosed in 30% infants. Its incidence was inversely associated with maternal disease duration (P < 0.05). Newborns of thymectomized mothers showed lower rate of neonatal myasthenia compared to those of non-thymectomized women (P < 0.05). Conclusions: MG patients can have normal pregnancy and delivery but the course is unpredictable. Shorter disease history and infection predispose to puerperal exacerbation. Maternal thymectomy lessens the likelihood of neonatal myasthenia. An interdisciplinary approach is required for managing the pregnant women with MG.

Keywords: Myasthenia gravis; Pregnancy; Myasthenia gravis, neonatal

1. Introduction

Myasthenia gravis (MG) is an autoimmune disorder affecting the neuromuscular junction. It may considerably affect the course of the pregnancy and cause serious complications in both the mother and the infant [1]. Fluctuating fatigue and progressive muscular weakness upon repeated movements are prevailing in clinical feature. Antibodies to nicotinic acetylcholine receptors (n-ACh-R) are the cause of the disturbant nerve impulse transmission to muscle fibers. Those antibodies belong to IgG immunoglobulin group. They may cross placenta and cause transitory neonatal myasthenia gravis (TNMG).

MG is relatively frequent among women of reproductive age (1:10,000 down to 1:50,000) so the obstetrician will certainly meet such patients sooner or later. The impact of pregnancy on the MG course is a subject of numerous reports [2–4]. Generally, in one third of the pregnant women the disease exacerbates, whereas in two third it shows no changes. More or less severe deterioration may develop in the first trimester. MG signs and symptoms in pregnant women tends to improve throughout second and third trimester coinciding with immunosuppression which normally takes place in that period. A complete remission occurs in some patients. The body’s immunological response reactivates again at time of delivery and in puerperium as well. This may be the cause of an exacerbation and deterioration of MG. The outcome of earlier pregnancies does not help in predicting the course of the current pregnancy or the future ones [3] The disease is not associated with sterility, yet a considerably higher incidence of spontaneous abortions does exist in the observed MG patients. No data are available on the increased incidence of premature labors or preeclampsia in pregnant women suffering from MG [5,6].

TNMG is a transitory form of myasthenia occurring in 12–20% of infants born to myasthenic mothers [7]. The clinical features of TNMG develop in the first 4 days of life: in two thirds of the cases the syndrome develops within a few hours after birth, and in 8% of the cases within the first day of life [8]. The symptoms usually last for 3 weeks. TNMG develops due to placental transfer of the nicotinic acetylcholine receptor antibodies from maternal to fetal blood circulation. A correlation occurs between a drop in antibodies titer and the infant’s muscular strength. The reason for a delayed onset of MG in the infant is an anticholinesterase drug, passing through the placenta, so that neonatal myasthenia...
is manifested only after the drug is excreted and decomposed in the infant. The TNMG signs are lethargy, slow respiration, faint cry, generalized muscular weakness and absence of Moro’s reflex. The infants show difficulties in sucking and breathing. The diagnosis can be confirmed by 0.05–0.1 ml edrophonium chloride (Tensilon, Roche, Basel, Switzerland) administered subcutaneously. In case of a remission, the diagnosis is confirmed and the infant is to be treated with acetylcholinesterase inhibitors. Appropriately treated, TNMG has the favorable outcome today [9]. It is remarkable that the mother’s disease gravity is not accompanied by the development of TNMG [4].

The purpose of this study is to review our experience with 65 MG patients and course of their 69 pregnancies. We have focused on MG signs and symptoms deterioration, incidence of obstetric interventions during labor, and incidence of transitory TNMG.

2. Material and methods

From 1972 to 1999, 65 patients with MG and a total of 69 pregnancies were treated and delivered at the Department of Gynecology and Obstetrics, University Hospital Center, Zagreb. The course of pregnancy, labor and puerperium were analyzed retrospectively, as well as the neonatal period in 70 infants born to MG mothers (two pregnancies involved twins, whereas one ended as miscarriage). Data were collected from patients’ medical documentation.

The diagnosis of MG was established at the Department of Neurology, University Hospital Center Zagreb. Regular check-ups during pregnancy were performed both at the Department of Neurology and the Department of Gynecology and Obstetrics. According to clinical signs and symptoms of the disease, patients were divided in the following groups: ocular, mild, moderate, and severe form of MG.

The transitory TNMG diagnosis was assessed on the basis of the clinical signs as general hypotonia, sucking disturbances, weak crying and respiratory difficulties and was confirmed by Tensilon test. The n-ACh-R antibodies were assayed 10 days after delivery.

Statistical workup included mean values, standard deviation, difference between arithmetic means. \( \chi^2 \)-test and analysis of variance.

3. Results

The average age of the patients was 28.0 ± 4.7 years, (range 21–41 years). Thirty-eight (55%) were para I, 20 (30%) were para II, 10 (14%) were para III, and 1 (1.4%) para IV.

In 36 (52.2%) patients MG lasted less than 5 years, nine of them developed the disease with the onset of pregnancy. In 19 (27.5%) MG lasted between 5 and 10 years, and in 14 (20.3%) over 10 years.

Seven (10.7%) patients had ocular form, 21 (32.3%) had mild, 29 (44.6%) had moderate and eight (12.3%) had severe form of the disease. Furthermore, we observed the overlapping of immunological disorders: three of our patients developed Hashimoto thyroiditis. Two of them reacted with hyperthyroidism and one with hypothyroidism.

Sixteen patients (23.2%) were free of therapy due to their complete remission of MG. Thirty (43.5%) were treated with acetylcholinesterase inhibitor (pyridostigmine) only and the other 23 (33.3%) patients were treated with pyridostigmine together with corticosteroids (prednisone). Prednisone was administered in high single dose given in alternate days. The dosage of prednisone was between 10 and 80 mg given each 2 days, depending on severity of myasthenic signs and symptoms. Nine patients were also treated with plasmapheresis in the last 2–4 weeks of pregnancy due to the significant deterioration of the disease. Three patients with unplanned pregnancy also had received azathioprine. Immediately after the confirmation of pregnancy azathioprine was omitted. Otherwise, azathioprine was omitted 6–12 months before the planned conception. The transsternal thymectomy was performed in 25 (38.5%) patients. Nine patients in this group were able to discontinue taking pyridostigmine after the surgery.

The majority of analyzed pregnancies resulted in term deliveries (after 37 weeks gestation). One miscarriage at 16 weeks gestation was observed. There were five premature births; three at 36 weeks and one at 34 and 35 weeks, respectively. The average duration of the pregnancies was 38.7 ± 2.6 weeks. The patients were usually admitted to hospital 2–4 weeks before the expecting term of the delivery to enable continuous monitoring.

Most labors (57; 82.6%) were completed vaginally. The vacuum extractor was used six times (8.7%), out of which two times due to a rotation anomaly and four times in attempt to shorten the second stage of labor. Twelve pregnancies (17.4%) were terminated by cesarean section. Only once cesarean section was made because of an exacerbation of myasthenia at 37 weeks gestation. That case occurred before we introduced plasmapheresis as a method of MG treatment. In all other cases the indications for cesarean were exclusively obstetrical (three times fetal asphyxia, four times breech presentation, and one occurrence each of multiple pregnancy and breech presentation of the first twin, eclampsia, placenta previa and repeated cesarean). In six women, labor was induced upon the proving of fetal maturity.

At the beginning of labor, oral administration of pyridostigmine was replaced with 2.0 mg pyridostigmine given intramuscularly. The patients continue receiving prednisone. When necessary, an extra dose of 50–100 mg prednisone was administered intramuscularly in the first stage of labor. In four patients, plasmapheresis was performed due to MG deterioration immediately after the delivery.

Ten patients (14.5%) developed MG deterioration in pregnancy (in last 4 weeks of pregnancy) and 11 (15.9%) during the puerperium; total 21 (30.4%) exacerbations
occurred. Other patients’ status remained unchanged (31, 22.3%) or even improved (17, 24.6%).

MG deterioration developed in all patients with severe and 13 patients with moderate generalized form, but only one patient experienced myasthenic crisis. It is useful to point out that the duration of MG in patients with an exacerbation during the puerperium amounted to 2.7 ± 2.4 years, whereas the duration in pregnant women who had no exacerbations during the puerperium averaged 6.3 ± 4.7 years. The difference is statistically relevant (P < 0.05).

The complications in the puerperium included two cases of endometritis and one case each of acute pyelonephritis, cystitis and mastitis. All women with puerperal infections developed exacerbations.

One patient who developed the first signs and symptoms with the onset of pregnancy developed severe deterioration of MG in the third trimester. At that time plasmapheresis was not included in MG treatment yet. This pregnancy was terminated by cesarean section employing the epidural anesthesia. After that the patient developed severe myasthenic crisis with respiratory insufficiency. The help of respirator was necessary as well as treating with high doses of prednisone and pyridostigmine. The newborn girl developed TNMG that lasted 3 weeks. Mother and newborn, both, recovered successfully.

In patients with puerperal exacerbation of MG the labor was not more frequently terminated surgically, by a cesarean section or vacuum extractor than in the patients who had spontaneous, vaginal deliveries.

The average newborns’ body weight was 3345 ± 768 g. Three newborns were below 10 centile and nine above 90 centile. The average 1 and 5 min Apgar scores were 9.6 ± 0.9 and 9.8 ± 0.6, respectively. One infant died in the early neonatal period, while the others were discharged as healthy.

The nonspecific hyperbilirubinemia occurred in 14 (20.0%) infants. Infants born to mothers who received pyridostigmine combined with prednisone during the pregnancy were more susceptible to nonspecific hyperbilirubinemia (9/23; 39.1%) than the infants born to mothers who were free of therapy or received pyridostigmine only (7/47; 14.9%). Comparison between those two groups revealed statistically significant difference (P < 0.05).

TNMG was observed in 21 newborns (30.0%). In 10 of them n-ACh-R antibodies were assayed and found positive 10 days after delivery. An inversely proportionate relation was found between the incidence of TNMG and the maternal disease duration. The average maternal disease duration was 4.9 ± 3.8 years in infants with TNMG, and 6.7 ± 4.6 years in infants without TNMG. Analysis of variance gave statistically significant difference (P < 0.05).

The n-ACh-R antibodies were assayed in 29 (44.6%) women. Twenty-one (72.4%) of them were seropositive and eight (27.6%) were seronegative. Only one (4.8%) patient in seropositive group had mild form of MG but her newborn developed very severe form of TNMG that lasted 3 months and was complicated with respiratory failure. Twelve (57.1%) seropositive patients had moderate form of MG. Nine of them were thymectomized previously. Two of them gave birth to newborns which developed mild form of TNMG, while the third newborn died due to cardiac arrest 2 days after birth. The autopsy was not performed upon the request of the parents. Eight (38.1%) seropositive patients had severe form of MG and six of them were thymectomized. Mild to moderate form of TNMG was diagnosed in two newborns born from mothers from this group. Eight seronegative patients had mild to moderate form of MG and none of newborns developed signs of TNMG. Newborns whose mothers underwent plasmapheresis in pregnancy (N = 9) showed no TNMG. Furthermore, in the group of newborns from thymectomized mothers (N = 25) only two of them (8%) developed the clinical features of TNMG. Comparison with non-thymectomized group (19/45, 42.2%) gave statistical significance (P < 0.05). TNMG was successfully treated with acetylcholinesterase inhibitors.

Nursing data were available for 33 patients: 25 of them (75.8%) were nursing successfully while 8 (24.2%) were not.

4. Comment

Recent references dealing with present topic mostly consist of reports on single [10] or low-number [11,12] cases, hence our reliance on earlier reports for a better insight.

In 22 myasthenic pregnant women, with a total of 33 pregnancies, Osserman showed that in one third of the pregnant women an exacerbation occurred, whereas two third showed no change or a remission occurred [2]. The exacerbation usually occurs during the first trimester, with minor changes during the second and third trimesters.

Plauche reported 113 MG patients with 164 pregnancies [13]. Antepartal exacerbations occurred in 35.4% of these pregnancies. In that period there were 14 spontaneous abortions, 14 therapeutic abortions, 12 cases of perinatal deaths and six maternal deaths.

The influence of pregnancy on MG is unpredictable [14]. As reported by Scott, the MG mothers mortality risk is inversely proportionate to the duration of the disease, the highest risk being in the first year and the minimal risk 7 years after the onset of the disease [15]. The spontaneous abortion is usually followed by a remission, unlike the situation after induced abortions. MG is not an indication for the termination of pregnancy. Among our patients, 11 had one or more induced abortions, but not related to their primary disease.

The possibility of the overlapping MG and some other autoimmune disorders is very common and well established. The Hashimoto thyroiditis is the most often autoimmune condition overlapping with MG.
Intrapartal care comprises careful preparation of the patient for labor, as well as team work of obstetricians, neurologists, anesthesiologists, neonatologists and nurses who would monitor the patient. There is no need to terminate the pregnancy before the term, and the cesarean delivery is performed if required by standard obstetric indications. The course of labor does not change in myasthenic patients, although shortened labors due to generalized relaxation are reported [16]. The use of the vacuum extractor is recommended to ease the second labor stage. We applied vacuum extractor in our patients much more frequent (8.7%) than we do in the general parturient women population (about 2%). The frequency of the cesarean delivery in parturient women with MG was also higher (17.4%) in relation to the general frequency of the cesarean delivery (11%) in the studied period.

During the labor, oral application of acetylcholinesterase inhibitor should be replaced with parenteral administration: 2.0 mg of pyridostigmine intramuscularly is recommended every 3–4 h. The parenteral administration of prednisone is also recommended to keep the muscle strength. Appropriately treated MG will enable the labor progression without any effect on the muscle strength. Administering of edrophonium may be useful in certain cases. Neostigmine is usually avoided because of its strong muscarinic and nicotinic side effects. The use of analgesics, tranquilizers, narcotics and magnesium sulfate should be avoided due to their negative effect on neuromuscular junction. The use of epidural anesthesia is encouraged in both modes of delivery, vaginal (relieves the pain from uterine contractions and reduces fatigue) and operative [12,17]. Vaginal mode of delivery dominated among our parturient women, which is in line with the experience of other authors [13]. Local anesthetics can be used, but high doses should be avoided because they may interfere with neuromuscular transmission. When local anesthesia is applied, high doses of ester anesthetics should be avoided.

Vacuum extraction and cesarean section were performed almost exclusively on account of obstetric indications, and just in one case because of MG exacerbation. Accordingly, we consider delivery of well-treated MG patient entirely on a par with a delivery of healthy woman.

The first 3 weeks following parturition are especially dangerous for MG patients, since in one third of such patients exacerbations occur that may be sudden and heavy [13]. Regardless of the mode of delivery, careful monitoring and adequate therapy are required. In postpartal period the patients will continue with the acetylcholinesterase inhibitor dose equal to the one taken before pregnancy if no deterioration was noticed. The principal rule in MG therapy is that the dose and kind of medicaments and other therapeutic procedures need to be adapted according to the sudden condition of the patient. Plasmapheresis and high doses of prednisolone were the most successful treatment in prevention of myasthenic crisis development. Puerperal infections (endometritis, mastitis, urinary tract infections) require immediate treatment. Otherwise, they may provoke severe deterioration of MG, which happened in some of our patients. A puerpera needs rest.

Nursing is permitted to the mothers with MG. Piridostigmine, as well as the nicotinic acetylcholine receptor antibodies, can be found in mother’s milk, but only in negligible amounts. Nursing is sometimes disrupted to avoid exhausting of the mother, but it must be done very cautiously because otherwise MG may deteriorate.

In three patients delivery followed few hours after plasmapheresis, in one patient 6 and in two 24 h later. This procedure probably lowered n-Ach-R antibody titer in newborns’ circulation also. Accordingly, it was expected that these infants will not develop the clinical signs of TNMG. The previous removal of mother’s thymus had a similar protective effect.

In conclusion, MG patients can have normal pregnancy and delivery. Deliveries are more often terminated by vacuum extractor to shorten the second labor stage. Pregnancies are terminated by cesarean section if there are obstetric indications. Only exceptionally serious MG exacerbation could be an indication for cesarean. The mode of delivery seemed not to affect the incidence of an exacerbation during the puerperium.

The course of MG in pregnancy is unpredictable. However, exacerbation in puerperium is more likely to occur in patients with shorter history of the disease. Also, puerperal infection seems to be predisposing factor for an exacerbation.

Close cooperation is required between obstetricians, neurologists, anesthesiologists and neonatologists managing the pregnant woman with MG and their newborns. Such care should be provided in appropriately equipped institutions with well-trained staff.

References