Paper I

CME

Myasthenia gravis

Consequences for pregnancy, delivery, and the newborn

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Abstract—*Objective:* To investigate the effect of maternal myasthenia gravis (MG) on giving birth and on the newborn. *Methods:* A retrospective cohort study for 1967 through 2000 was undertaken, using data from the Medical Birth Registry of Norway, based on the compulsory notification of all births. The target group consisted of 127 births by mothers with MG. The reference group consisted of all 1.9 million births by mothers without MG. *Results:* Women with MG had a higher rate of complications at delivery (40.9% vs 32.9%, $p = 0.05$), and in particular the risk of preterm rupture of amniotic membranes was three times higher in the MG group compared to the reference group (5.5% vs 1.7%, $p = 0.001$). The rate of interventions during birth was raised (33.9% vs 20.0%, $p < 0.001$) and cesarean sections doubled (17.3% vs 8.6%, $p = 0.001$). Five children (3.9%) born by MG mothers had severe anomalies, and three of them died. *Conclusions:* MG is associated with an increased risk for complications during delivery. This is linked to a higher occurrence of interventions during birth.

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There is a two-way relationship between pregnancy and autoimmune disease: maternal changes in pregnancy can affect the disease, but the disease can also affect the outcome of pregnancy and the child.[1] The main points are that the child is grafted onto the mother, and that immunoglobulin (Ig)G antibodies cross the placenta whereas IgA and IgM do not. Thus a disease mediated by IgG can affect the child in utero or neonatally. About 15% of infants born to women with myasthenia gravis (MG) are thought to develop neonatal MG. The symptoms are usually mild or moderate, including poor sucking and generalized hypotonia.[2] Due to degradation of the maternally derived IgG, the effect upon the infant will be transient, except if the damage caused is irreversible.

As for autoimmune disease in general, the effect of pregnancy is variable. Rheumatoid arthritis usually improves during pregnancy, but the occurrence of intrauterine growth retardation is a common feature of all autoimmune diseases and the etiology is multifactorial.[1] For patients with MG, an increase in maternal mortality, morbidity, pregnancy wastage, and premature labor has been reported.[3] Pregnancy does not worsen the long-term outcome of MG,[4] but the disorder sometimes becomes manifest during pregnancy or postnatally.[5] The first trimester and the postpartum period appear to be the most critical periods for MG exacerbation.[6]

The aim of the current study was to examine the effect of pre-existing MG on delivery and the newborn. The weakness of striated muscle could cause a prolonged delivery phase with increased risk for both mother and child. To examine to what degree this is true, we collected data from the Medical Birth Registry of Norway (MBRN). These data represent a complete national survey of births in Norway from 1967 onward.

Materials and methods. *Medical Birth Registry of Norway.* MBRN was established in 1967 and is based on the compulsory notification of all births after 16 weeks of gestation. The notification form is sent within 9 days after birth or discharge from the institution. The registry contains data on the mother's demographic variables, the pregnancy, the delivery, and the newborn. An unchanged birth notification form was in use from 1967 through 1998. A revised and more detailed form has been used since December 1, 1998, which includes a record of drugs used by the mother before and during pregnancy. Complete ascertainment of the births is ensured through a record linkage with the National Population Registry run by Statistics Norway. The registry is placed under the Norwegian Institute of Public Health.

Patients with MG and reference group. The data material comprised births registered in MBRN between January 1, 1967, and December 31, 2000. Patients with MG were defined as women in whom the MG diagnosis was noted in the birth notification form. A total of 127 MG births by 79 patients occurred in the period. The reference group consisted of all births by women without a diagnosis of MG (n = 1,988,865).

Birth notification form. The information in the birth notification form is based on three elements: 1) a standardized form used during pregnancy by the patient's physician, 2) oral information given by the patient when admitted to the hospital, and 3) information from doctor and midwife about the actual delivery and the newborn. Thus, the notification form contains information on the mother's health before and during pregnancy as well as information about the actual birth and the newborn. Completion of the

See also pages 1326 and 1459

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Table 1 *Patient demographics*

Characteristic	Women with MG	Reference group	*p* Value*
No. of deliveries	127	1,988,865	—
Mean maternal age, y	29	27	<0.001
Mean birth order	1.9	1.9	0.5
Birth at university hospital (%)	68 (53.5)	501,959 (25.2)	<0.001
Mean gestational age, wk	39.4	39.6	0.5
Mean birthweight, g	3,483	3,485	1.0
Thymectomy	45 (35.4)	—	—

* Pearson χ^2 *p* value.

MG = myasthenia gravis.

notification form is the responsibility of the attending midwife. The form is cosigned by the attending physician.

Variables. Descriptive variables included year of birth, type of obstetric institution, age of mother (completed years), sex of child, birth order/parity, birth weight in grams, and gestational age in completed weeks. Thymectomy was included as a descriptive variable for women with MG. Outcome variables included induction of birth (perforation of amniotic membranes and/or infusion with oxytocin and prostaglandin), interventions (any intervention, perforation of amniotic membranes, caesarian section, use of vacuum extractor or forceps, and manual removal of placenta), complications (any complication, premature rupture of amniotic membranes, functional disorder of birth, injuries in the birth canal, bleeding postpartum, obstruction of birth process, and complications regarding the umbilical cord), perinatal mortality, congenital conditions, and birth defects of the newborn. After 1988, cesarean sections were classified as elective or not. Perinatal mortality was defined as all fetal deaths after 16 weeks of gestation as well as deaths during the first week of life. The birth defects were defined as severe or not severe, according to a definition by MBRN based on International Classification of Diseases (ICD)-8 (1967 through 1998) and ICD-10 (1999 through 2000). Medication during pregnancy was only sporadically recorded in the MBRN before 1999, but we were able to retrieve this from the hospital journals in cases where birth defects occurred. From 1999 onward, medication was recorded on the MBRN form.

Statistics. Cross tables with Pearson χ^2 test were used to compare the MG and the reference groups. Two-sided *p* values less than 0.05 were used to indicate significance. To detect trends in obstetric care and management of patients with MG, the material was subgrouped into the following periods of time: 1967 through 1980, 1981 through 1990, and 1991 through 2000. Arithmetic mean was calculated for each group regarding gestational age, mother's age, and parity. The analyses were based on crude, stratified, and adjusted measures. Mother's age in completed years at birth (<25, 25 through 29, 30 through 34, 35+ years), period of birth (1967 through 1980, 1981 through 1990, 1991 through 2000), and birth order (one, two, three or more children) were considered as potential confounders. Confounding was evaluated in unconditional logistic regression analyses with all variables represented as categorical variables. We also stratified for type of birth institution (university hospital, other) to see if the results varied according to type of institution.

Results. A total of 127 births occurred in 79 women with MG (table 1). The distribution according to period of birth was 39 births 1967 through 1980, 37 births 1981 through 1990, and 51 births 1991 through 2000. Mean maternal age was higher in the MG group than in the reference group. A majority of patients with MG gave birth at university hospitals. Mean gestational age, mean birth order (parity), prematurity, and mean birthweight did not differ between the two groups. Among the 79 women with MG, 43 were recorded with one birth, 28 with two births, 5 with three births, 2 with four births, and 1 woman with five births. Six of the 11 women (54.5%) giving birth in 1999 through 2000 received medication during pregnancy. All used pyridostigmine (Mestinon) only.

Intervention during birth occurred more frequently in the MG group than in the reference group (table 2), but the number of births requiring induction (infusion of oxytocin or Pitocin, perforation of amniotic membranes) was not significantly raised in the MG group. The rate was 16.5% vs 13.4% in the reference group ($p = 0.3$). Except for operative delivery and forceps/vacuum no single intervention procedure was performed significantly more often in the MG group.

The total use of operative delivery was relatively stable in the MG group over time (table 3). There was a marked difference between the MG group and the reference group in the first time period. The increased use of cesarean section in the reference group over time diminished this difference. Cesarean section occurred more often in the

Table 2 *Intervention during labor and obstetric complications*

Procedure	MG group, n (%)	Reference group, %	Rate ratio	*p* Value*
Total intervention during birth	43 (33.9)	20.0	1.7	<0.001
Cesarean section				
Total	22 (17.3)	8.6	2.0	0.001
Elective†	11 (17.2)	4.6	3.7	<0.001
Vaginal intervention (forceps/vacuum)	11 (8.7)	6.3	1.4	0.4
Total occurrence of complications	52 (40.9)	32.9	1.2	0.05
Preterm rupture of amniotic membranes	7 (5.5)	1.7	3.2	0.001
Functional disorder of birth	12 (9.4)	6.5	1.4	0.2
Injuries in birth canal	8 (6.3)	3.7	1.7	0.1
Bleeding postpartum	7 (5.5)	5.3	1.0	0.9
Obstruction of birth process	2 (1.6)	2.0	0.8	0.8
Umbilical cord complications	17 (13.4)	12.6	1.1	0.8

* Pearson χ^2 *p* value.
† Only births 1988–2000.

MG = myasthenia gravis.

Table 3 *Operative delivery in the MG and reference groups according to period of birth (total operative deliveries = cesarean section plus forceps/vacuum)*

Procedure/period of birth	MG group, n (%)	Reference group, %	Rate ratio	*p* Value*
Total operative deliveries				
1967–1980	10 (25.7)	8.0	3.2	<0.001
1981–1990	8 (21.6)	18.0	1.2	0.6
1991–2000	15 (29.4)	20.0	1.5	0.1
Cesarean section				
1967–1980	4 (10.3)	3.6	2.9	0.03
1981–1990	5 (13.5)	10.9	1.2	0.6
1991–2000	13 (25.5)	12.8	2.0	0.007
Forceps and vacuum				
1967–1980	6 (15.4)	4.4	3.5	0.003
1981–1990	3 (8.1)	7.1	1.1	0.9
1991–2000	2 (3.9)	7.2	0.5	0.6

* Pearson χ^2 *p* value.

MG = myasthenia gravis.

MG group in all three periods, whereas the use of forceps/vacuum was significantly higher in the first period only (see table 3). In 6 of the 22 cases where cesarean section was performed, a functional birth disorder was noted. From 1988 it has been possible to distinguish between elective and emergency sections. Eleven of 13 cesarean sections in the MG group were classified as elective in this period, significantly more than in the reference group.

The total rate of complications was significantly raised in the MG group (see table 2), but preterm rupture of membranes was the only single complication noted to occur more often in the MG group. No significantly increased incidence was found regarding postpartum bleeding, obstruction of the birth process, functional disorder of birth, or injuries in the birth canal. Nor was there any difference for umbilical cord complications: 13.4% in the MG group vs 12.6% in the reference group ($p = 0.8$). Forceps/vacuum were used during birth in two of the seven cases where preterm rupture of membranes occurred. Cesarean section was not performed in any of these cases.

Birth defects and/or neonatal complications were noted in 27 (21.3%) of the 127 children. These were also the children who were transferred to a pediatric unit (table 4). In the reference group, 40,189 (2.0%) of the neonates were transferred to a pediatric unit. Five (3.9%) of the 127 MG children had birth defects that were classified as severe, compared to 1.9% in the reference group. Three children with severe birth defects died. Neonatal MG was diagnosed in five cases, none of them together with a congenital condition. The twins who died due to severe birth defects had the same mother as a newborn with severe neonatal MG. The mother had been thymectomized prior

Table 4 *Birth defects, neonatal conditions, and perinatal deaths among the 127 infants born by MG mothers*

Condition	No.	Perinatal deaths	Medication/thymectomy
Multiple birth defects, unspecified	1	Died <10 min after birth	Pyridostigmine
Deformed foot	1		Pyridostigmine
Deformity of lower limb and deformity of thorax*	1	Died during birth	
Deformity of muscles and skeleton and omphalocele*	1	Died <24 h after birth	Bromocriptine, pyridostigmine, thymectomized
Down syndrome	1		Pyridostigmine
Neonatal MG	5		‡
Erythroblastosis	2		‡
Icterus	1		‡
Cyanosis	1		‡
Luxation of hip joint	1		‡
Dysplasia of the hip joint	1		‡
Systolic murmur of heart	1		‡
Observed at a department of pediatrics†	10		‡

* Twinning pair.
† No further diagnosis made.
‡ No information available.

MG = myasthenia gravis.

to the birth of the twins. The four mothers who gave birth to children with severe birth defects had all used pyridostigmine during pregnancy.

In 10 (37.3%) of the 27 MG children who were moved to a department of pediatrics, no other diagnosis than observation was recorded on the birth notification form. Forty-five percent of the cases transferred to a pediatric unit in the reference group did not receive any other diagnosis than observation.

Perinatal mortality was 2.4% in the MG group vs 1.4% in the reference group ($p = 0.7$).

Thymectomy in the mother had been performed for 45 (35.4%) of the 127 MG births. In 16 cases, the mother was thymectomized prior to first pregnancy. The 45 births where the mother had been thymectomized were compared to the other 82 nonthymectomy MG births. No significant differences were found regarding birthweight, induction of birth, cesarean section, complications during birth, intervention during birth, birth defects, or premature rupture of membranes.

The impact of potential confounders was analyzed through logistic regression. Adjusted results did not differ from the crude results, and so the data presented are based on crude measures.

Discussion. This is the first population-based cohort study where the pregnancies and births of women with MG and conditions in their newborns have been compared to those of an extensive reference group in a time span of more than 30 years. The women with MG in this study had a significantly higher risk of delivery complications, and it was necessary to intervene during birth more frequently. Their risk of having a cesarean section was doubled compared to the reference group. Five children born to mothers with MG had serious birth defects, but this was not significantly higher than in the reference group (3.9 vs 1.9%). No significant differences were found regarding perinatal mortality, mean gestational age, birthweight, or parity.

There is convincing evidence that this study has included all women with MG giving birth in Norway from 1967 through 2000. Although the validity for the MG diagnosis is not specifically documented, a study of various rheumatic disease diagnoses (rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, and psoriatic arthritis) found that the proportion of cases in hospital databases (gold standard) registered in the MBRN—i.e., sensitivity—was 88.2%.[7]

The specificity of the diagnosis is more important, as false positives tend to dilute any effects. We have been able to link data on each mother's consecutive births. The linkage showed a high consistency in the diagnosis of MG for consecutive births, suggesting no or a very low proportion of false positives in our data set.

MG is a very distinctive diagnosis, used by patients and doctors only when positively verified. It is a condition known to affect pregnancy and delivery. Maternal conditions considered more clinically important, requiring high-quality care, are notified with a higher ascertainment than conditions considered of little clinical importance.[8] The prevalence of MG is estimated at about 1 in 10,000.[9-11] With a Norwegian population of 4.5 million, an equal incidence of MG in male and female patients,[12] and an increased incidence above 60 years, our number of 79 childbearing women with MG could well represent the whole target group in the actual period. The prevalence of MG births in this study was 6.4 in 100,000.

The total rate of complications was raised among women with MG, but preterm rupture of the amniotic membranes was the only single complication to occur more frequently. An increased risk of preterm rupture has also been reported in patients with other autoimmune disorders.[13,14] The etiology of the rupture is not clear; it might be an effect of medication, preferably steroids, or be related to the disease process. Pyridostigmine, which is the first drug given to patients with early onset MG, is not associated with higher incidence of this condition.[15] Preterm rupture of amniotic membranes facilitates ascending infections, causing amnionitis, which comprises a great risk for mother and child. When preterm rupture occurs, the patient must be admitted to the hospital, confined to bed, and, if necessary, given medication. In some cases, delivery must be induced.[16] Preterm rupture of membranes did not lead to cesarean section in our patients and therefore does not explain the increased rate of sections among the patients with MG.

The total number of cesarean sections was significantly higher in the MG population than in the reference group. This is in contrast with a study from Italy,[4] but in agreement with a study from Croatia.[17] The policy in Norway toward cesarean section has been restrictive; in 1973, it was performed in only 2.5% of all deliveries. The rate increased to 13.6% in 1998,[18] but was still substantially lower than in most other western countries.[19-21] A low total rate of cesarean section implies that specific risk groups are more likely to have a higher rate than the general population.

The increase in the use of cesarean section over time was more pronounced for the MG group than for the reference group. Simultaneously there was a decrease in the use of forceps and vacuum. This probably reflects increased awareness of the problems that women with MG may have during delivery. The high rate of elective cesarean sections in the MG group could have prevented some of the complications related to vaginal delivery. Through the increased use of epidural anesthesia and thromboprophylaxis, the risk of cesarean sections has been reduced. A large fraction of mothers with MG delivered at university hospitals. University hospitals tend to have a higher load of births with special needs, requiring surgical intervention. But although the overall cesarean section rate in our study was higher at university hospitals, the tendency to perform cesarean section on patients with MG was strongest in other hospitals.

The number of severe birth defects was not significantly raised in the MG group. Our figure is higher than reported in a similar study.[4] The three children who died all had skeletal anomalies. These anomalies could represent features of fetal arthrogryposis, a condition that can be caused by placental transfer of maternal anti-AChR antibodies.[22] It is vital for normal development of joints to be able to move freely from 7 to 8 weeks of gestation and onward. If movements are restricted as an effect of maternal anti-AChR antibodies, anomalies can occur. The transplacental transfer of antibodies could explain why the mother of the twinning pair with abnormalities later gave birth to a child severely affected by neonatal MG.

Information on medication was not recorded on the MBRN form in the years 1967 to 1998, and could therefore not be presented in this study. We were, however, able to retrieve information from the journals of the mothers who had given birth to children with severe birth defects. Information on medication was also found in the revised MBRN form for the years 1999 and 2000. Pyridostigmine was the only drug used for MG in these pregnant women. Pyridostigmine belongs to class C in the Food and Drug Administration classification system regarding teratogenicity, teratogenic risk undetermined. Malformations were seen in rats when given in a very high dose, also producing maternal toxicity.[23] No epidemiologic studies of congenital anomalies have been reported.[24]

Information on disease severity is not recorded in the MBRN forms. However, previously performed thymectomy implicates a generalized and more severe form of MG. No increased risk for complications was found in the thymectomized patients. This indicates that MG severity is not a critical factor. Alternatively, the improvement induced by a previous thymectomy may explain these results.[25,26] Thymectomy does not represent a risk factor for pregnancy, delivery, or the newborn.

Neonatal mortality did not differ significantly between the MG group and the reference group, nor was there a higher rate of prematurity among the MG group. Mean gestational weight, which has been reported reduced for mothers with other autoimmune diseases,[27] did not differ between the two groups in our study.

The incidence of neonatal MG has been estimated between 10% and 21%.[1-3] In our study, neonatal MG was noted in only 4% of the newborns, but another 8% was observed in a pediatric unit without any diagnosis recorded at birth. Up to 12% with neonatal MG might therefore be assumed. Symptoms such as poor sucking and hypotonia can be related to numerous causes and specific treatment is usually not required. Retrospective studies probably underreport this condition.

MG is a chronic disease. This may give potential mothers reason to worry about pregnancy, birth, and caring for a child. The significantly higher mean age at pregnancy in the MG group may suggest that pregnancies in this group are better planned. But previous pregnancies, deliveries, and motherhood do not seem to frighten off women in the MG group, as there was no significant difference in parity between the two groups.

We found that MG affects the birth process as well as the newborn. Thus, the pregnant woman with MG remains a challenge both for the obstetrician and the neurologist. Future studies should concentrate on identifying mothers with MG who are particular at risk to see if special management applied would improve outcome in those cases.

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