Paper III

Myasthenia gravis in pregnancy and birth:

Identifying risk factors, optimising care

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Word count: Title: 83 (with spaces). Abstract: 193 words. Article: 2482 words. References: 22

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Keywords: Myasthenia gravis, neonatal myasthenia gravis, pregnancy, delivery, thymectomy

Abstract

Women with myasthenia gravis (MG) have increased risk of pregnancy complications and an adverse pregnancy outcome. This study examined risk factors for such complications in order to improve the care for pregnant MG women. Through the Medical Birth Registry of Norway, 73 MG mothers with 135 births were identified. Their obstetrical and clinical records were examined. Data on pregnancy, delivery and the newborn were combined with information on mother's disease. The risk for neonatal MG was halved if the mother was thymectomised (P = 0.03). Children with neonatal MG were more likely to display signs of fetal distress during delivery (P = 0.05). Only in one-third of the pregnancies did the patient see a neurologist during pregnancy. These patients used MG medication more often during pregnancy (P = 0.001), and were more likely to be thymectomised (P = 0.007). They also had a higher rate of elective sections (P = 0.005). Thymectomy may have a protective effect against neonatal MG. Neonatal MG can cause fetal distress during delivery. Most MG women benefit from being examined by a neurologist during pregnancy, to minimise risks and select the best delivery mode in collaboration with obstetricians.

Introduction

Early onset MG with thymic hyperplasia, high acetylcholine receptor (AChR) antibody

concentration and no other muscle antibodies is the dominant MG subtype among women in

fertile age [1]. Pregnancy does not worsen the long-term outcome of MG, but the disorder

sometimes becomes manifest during pregnancy or postpartum [2,3]. The first trimester and

the postpartum period represent the most critical phase for exacerbations [4].

MG is associated with an increased rate both of complications and operative

interventions during delivery [5]. The complication rate is increased also in asymptomatic

MG [6]. Transplacental transmission of IgG antibodies can lead to neonatal MG, which

affects 10-20% of children born to MG mothers [2,7]. Symptoms of neonatal MG consist

mainly of transient respiratory problems and difficulties in feeding and swallowing. It is

important that these children are observed and treated optimally. Maternal MG is also a rare

cause for arthrogryposis multiplex congenita, a congenital disorder characterized by multiple

joint contractures and other anomalies, probably resulting from lack of movement in utero [8].

Both conditions can occur in offsprings of women with very little symptoms or where MG is

not yet diagnosed [6, 9].

In this study, we identified all MG mothers who had given birth in Norway during the

last 36 years. Detailed obstetrical and clinical records were collected for 135 births in 73

women. Data on pregnancy, delivery and the newborn were combined with information

regarding mother's disease in order to identify factors responsible for the increased

complication rate.

Material and methods

Medical Birth Registry of Norway

The Medical Birth Registry of Norway (MBRN) was established in 1967 and is based on the compulsory notification of all births in Norway after 16 weeks of gestation. The notification form is sent within 9 days after birth or discharge from the hospital. The registry contains data on the mother's demographic variables, the pregnancy, the delivery and the newborn. The registry is placed under the Norwegian Institute of Public Health.

The MG-diagnosis in MBRN

Diseases of the mother, both before and during pregnancy, are recorded on the birth notification form and coded according to ICD-8 (until 1998) and ICD-10 (1999 and onwards). Disease severity is not recorded. The information is based on three elements: 1) a standardised form used by the patient's physician during pregnancy, 2) oral information given by the patient when admitted to the hospital, 3) information from the attending doctor and midwife about the delivery and the newborn. Previous studies have concluded with a high diagnostic validity in the MBRN [5,10].

Patients

90 women recorded with the diagnosis MG in one or more deliveries between 1967 and 2004 were identified through the MBRN. On behalf of the project, MBRN contacted each woman by mail and asked for permission for Dr. Midelfart Hoff to examine the obstetrical records for all their deliveries as well as the records for the newborn and the birth protocols. 80 (89%) women replied and 79 women confirmed their MG diagnosis and enclosed a written consent.

One woman claimed that she had never had MG. Among the ten who did not reply, one was confirmed dead, and in four cases their current address was unknown.

In cases of consent, the hospital where the woman had given birth was identified and the head of the obstetrical department was asked for the following information: The full obstetrical records with special emphasis on any consultations by neurologists, paediatricians and anaesthesiologists, the record for the newborn and the birth protocols. Information was obtained for 135 births in 73 women. In the cases where obstetrical records could not be obtained, despite repeated inquiries, this was either because the hospital had outsourced its eldest record material or because the record could not be found.

Data on the course of pregnancy, labor and puerperium as well as the neonatal period were retrieved from the obstetrical records and analysed retrospectively. Data on disease activity during pregnancy could only be found in a few records, but was recorded when present. The protocol of this study was approved by the regional ethical committee.

Statistical methods

The following subgroups were examined: 1) Thymectomy prior to delivery, 2) Seen by a neurologist during pregnancy, 3) Additional autoimmune disease, 4) Use of MG medication before and during pregnancy 5) Deterioration of MG during pregnancy. Comparisons were performed using cross-tables with Pearsons chi-square statistics and in cases with n<5, Fishers exact test was used. Two-sided p values less than 0.05 were used to indicate statistical significance. The rate ratio was calculated as the ratio of the incidence among the groups to be compared. The statistical analysis was performed in SPSS (version 11.0; SPSS, Chicago, IL, USA).

Validity analysis

The following four variables were selected for a validity analysis of information in the MBRN: Intervention during delivery (yes/no, type of intervention), complications during delivery (yes/no, type of complication), neonatal MG, transfer to neonatal unit. Information in the MBRN was compared to the obstetrical records, which were regarded as the gold standard. The obstetrical records were linked to the data in the MBRN using the mothers' national identification number.

The MBRN sensitivity was calculated as the proportion of deliveries where factual information was given in the MBRN. Data was defined as incorrect when the information contrasted with the obstetrical records. Data on intervention was recorded correctly in 128 of 135 cases (95 % sensitivity). Data on complications was recorded correctly in 120 of 135 cases (89 % sensitivity). As for neonatal MG, 17 neonates were described in the obstetrical records as having verified or suspected neonatal MG – but only 9 cases were recorded in the MBRN (sensitivity 53%).

Results

135 MG births in 73 MG mothers occurred between 1967 and 2004 were included, 70 girls and 67 boys. Two women had twins. For 58 mothers, we had data on the first and consecutive births. For 10 mothers, we included data from the second and all further births, whereas for 5 mothers, we only obtained data from one later birth (third birth, fourth birth, sixth birth). Of the 58 mothers included with their first birth, 22 women had developed MG prior to their first pregnancy, in average six years in advance. Seven first-time mothers (12%) developed symptoms or were diagnosed during their pregnancy. In one of them, MG was unmasked when she received general anesthesia during delivery and post partum developed respiratory

problems, requiring intensive care. 29 of the first-time mothers were diagnosed with MG after this pregnancy.

One or more complications during pregnancy were reported in 28 (21%) pregnancies (Table 1). Deterioration of MG was reported in 13 (10%) cases. In one case, the deterioration was so severe that the woman had to give birth in a respirator. In 5 of these 13 pregnancies, the child had neonatal MG. Complications during delivery was reported for 40 of the 135 (30 %) pregnancies (Table 2). The most frequent complication was protracted labor/fetal distress (26 deliveries).

The newborn was observed in a neonate unit after delivery in 47 (35%) cases, decided by the attending pediatrician. Neonatal MG was suspected in 26 (19%) cases, among which five cases were identified on the basis of symptoms, verified through electrophysiological and antibody-testing, whereas 21 cases were not tested. Neonatal MG was less frequent if the mother had been thymectomised prior to delivery (13% vs. 27%, p= 0.003). Children with suspected neonatal MG were more likely to show distress and signs of hypoxia during delivery, manifested through meconium-stained amniotic fluid (31% vs. 15%, p= 0.05).

Thymectomy had been performed in 72 of the 135 pregnancies (Table 3). Except for neonatal MG, no significant differences were found for thymectomy versus no thymectomy regarding deterioration of MG during pregnancy, use of medication before and during pregnancy, complications and interventions during pregnancy and delivery. 25 of the 41 thymectomised women had undergone thymectomy before their first birth, in average five years before. Two patients were thymectomized during pregnancy, one developing asystolia during the procedure. She survived after open heart massage without any sequela, and so did her, at the time, 22-week-old fetus.

The mother was seen by a neurologist in 41 of the 135 pregnancies (table 4). These 41 cases were characterised by a higher occurrence of previous thymectomy, a higher use of MG

medication both prior to and during pregnancy and a higher frequency of caesarean section, in particular elective section. Newborns of these mothers were more frequently observed at neonate units after birth while no differences were found for complications during pregnancy and delivery or for neonatal MG.

12 (16 %) of the 73 women had experienced one or more spontaneous abortions, and three of them had three or more consecutive abortions (i.e. recurrent miscarriages). Two of these three women had an additional immunological disorder (thyreoiditis, rheumatoid arthritis) and also smoked heavily during pregnancy.

Additional immunological disorders were recorded in 10 of the 73 women. Four women had asthma and eczema, three thyreoiditis, one rheumatoid arthritis, one coeliaki, one alopecia areata, and one Crohn's disease. No differences could be found for these 17 cases compared to the group with no additional immunological disorder regarding complications during pregnancy and delivery, MG medication, neonatal MG or other conditions in the newborn.

MG medication was listed in the obstetrical record as used at the time of conception in 67 (50%) of the 135 pregnancies, that is in 68% of those with a MG diagnosis at the time It was continued throughout pregnancy in 61 cases (45%). None of the mothers started with MG medication during pregnancy. Pyridostigmine was used in 66 cases. One woman used corticosteroids. No women used other immunosuppressants. Additional treatment (plasmapheresis, respirator) for MG symptoms/complications was necessary in three cases. No differences were found between the 61 cases where medication had been used during pregnancy and the cases where it had not, regarding complications during pregnancy and delivery, neonatal MG or any other condition in the newborn.

Discussion

We have found that neonates of MG mothers who had undergone thymectomy were less likely to develop neonatal MG then those without thymectomy. It seems therefore that thymectomy has a protective effect against neonatal MG [11], probably by lowering the level of AChR antibodies, both the adult and fetal isoform. Thus, thymectomy should be recommended in women with generalized MG with a child wish, especially if they have already given birth to a child with neonatal MG. A further subject for research should be to see if this applies for arthrogryposis multiplex congenita as well. Thymectomy did not seem to prevent other complications during pregnancy and delivery.

Spontaneous abortions were reported in 12 of 73 (16 %) women in this study. A Danish prospective register study found the overall rate of spontaneous abortions to be 10.9 % in all pregnancies intended to be carried to term [12]. This indicates that the spontaneous abortion rate is not increased in MG patients.Even though the rate of spontaneous abortions is increased in some autoimmune diseases, this has not been verified for MG [2].

Newborns with neonatal MG were more prone to experience distress during the delivery process. Intrapartum fetal distress can be the first sign of a preexisting neurological condition [13]. Newborns of a MG mother should be carefully observed during the first post partum days for signs of muscle weakness and impaired respiratory and bulbar function, as the symptoms of neonatal MG usually are first displayed 12 - 48 hours after birth [14]. The clinical condition of the mother cannot be used to predict the risk for neonatal MG, as neonatal MG also may develop in newborns of mothers with little or no MG symptoms [6,9].

40% of the patients in this study did not use any MG medication. Of the 60% who used medication for their MG, the majority used pyridostigmine, and only one woman received immunosuppressive treatment. In this patient group of young females, thymectomy is usually undertaken before immunosuppressive drug treatment, and immunosuppressants

added only for persistent and progressive MG [15, 16]. However, the lack of use of immunosuppressants illustrates that many women in this study had mild or preclinical MG or were in clinical remission. 29 of 73 mothers in this study were diagnosed after their first birth. This must be taken into consideration when assessing the rates of complications during pregnancy and delivery, although as we have previously shown that also mild and preclinical MG can lead to complications [6]. Suboptimal treatment with immunosuppressants could on the other hand theoretically have increased the rate of MG-related complications due to higher AChR antibody concentrations. Information on MG severity would have been crucial to resolve this question, but could not be retrieved in a reliable way in this study.

Our findings also reflect the reluctance among physicians to prescribe - or women to use - drugs with possible teratogenic effects during fertile age. This caution in immunosuppressive drug-treatment of young, female MG patients is in accordance with findings in other studies [11]. Steroids used in the first trimester have been linked to increased occurrence of cleft palate, but have been considered safe for the rest of the pregnancy [17].

As for other immunosuppressants, their teratogenic potential are either not yet clear, such as for azathioprine - or definitely contraindicated in pregnancy or in anyone considering conception, as for methotrexate. Azathioprine has been linked to increased risk of malformations [18, 19], and MG women taking this drug might consider delaying pregnancy until disease improvement permits discontinuation or dosage reduction [20].

Only in one-third of the pregnancies did the women see a neurologist. The more frequent use of MG medication in this group, both prior to and during pregnancy, indicates that these patients were more severely affected by their disease, supported also by their higher rate of previous thymectomy. The more severe MG in these patients may explain why the follow-up by a neurologist did not seem to have any positive effect on complications during pregnancy and delivery.

Among the patients seen by a neurologist, both the rate of emergency cesarean section and elective caesarean section were raised. The increased proportion of elective section in this group of patients may reflect better planning regarding delivery mode, as elective sections are more favorable than emergency procedures in MG patients. This is mainly because emergency procedures often require general anesthesia, which is badly tolerated in MG patients [21]. One patient in our study got her MG unmasked after general anesthesia during caesarean section, and similar cases have been described previously [22]. The aim should be to minimize the need for emergency sections in MG patients. This could be done by monitoring MG activity during pregnancy, and in cases of deterioration or extensive MG weakness, elective section should be considered.

Increased awareness of MG as a risk factor for pregnancy and delivery should not discourage MG patients from giving birth, but lead neurologists to cooperate more actively with obstetricians and pediatricians in order to optimize the MG treatment and minimize the risks.

Table 1. Complications in MG-patients during pregnancy, related to neurologist follow-up and previous thymectomy.

Type of complication	Total number	Seen by neurologist	Thymectomy
Bleeding	5	2	2
MG deterioration	13	4	5
Preeclampsia	5	3	5
Infections	1	0	1
Growth retardation	4	2	2
Arthrogryposis	0	0	0
PROM	3	1	1

(PROM= Premature rupture of amniotic membranes)

Table 2. Complications in MG-patients during delivery, related to neurologist follow-up and previous thymectomy.

Type of complication	Total number	Seen by neurologist	Thymectomy
Protracted labor/fetal distress	26	6	11
PROM	8	1	4
Presentation anomalies	5	2	5
Bleeding >1500 ml	1	0	0
Abruptio placenta	1	1	1
Shoulder dystocia	1	0	1
Non-institutional deliveries	2	0	0

(PROM = Premature rupture of amniotic membranes)

Table 3. Thymectomy prior to delivery versus no thymectomy in MG mothers.

	Thymectomy (= 72)	No thymectomy (= 63)	P-value	95% CI	Rate ratio
	n (%)	n (%)			
Neonatal MG	9 (13)	17 (27)	0.03	0.16-0.94	0.4
Use of medication					
At conception	39 (54)	28 (44)	0.3	0.34-1.34	0.7
During pregnancy	35 (48)	26 (41)	0.7	0.38-1.47	0.7
Complications					
During pregnancy	17 (23)	11 (17)	0.6	0.55-3.03	1.3
During delivery	20 (27)	20 (34)	0.4	0.35-1.54	0.9
Interventions	23 (31)	24 (38)	0.5	0.38-1.55	0.8
Cesarean section	10 (13)	13 (20)	0.6	0.25-1.53	0.6
MG deterioration	6 (8)	7 (11)	0.6	0.23-2.29	0.7
Seen by neurologist	29 (40)	12 (19)	0.007	1.30-6.29	2.9

Table 4. Pregnancies in MG patients seen by neurologist versus not seen by neurologist

	Neurologist + (=41) n(%)	Neurologist ÷ (=94) n (%)	P-value	95% CI	Rate ratio
Thymectomy	29 (71)	43 (46)	0.007	1.30-6.29	2.9
MG medication during pregnancy	27 (66)	34 (36)	0.001	1.57-7.35	3.4
Complications during pregnancy	11 (28)	17 (19)	0.3	0.68-3.93	1.7
Caesarean section	13 (32)	10 (10)	0.003	1.54-9.87	3.9
- Elective	7 (17)	3 (3)	0.009*	1.53-25.6	6.25
Neonatal MG	11 (27)	15 (16)	0.1	0.80-4.68	1.9
Newborn to neonate unit	22 (60)	25 (28)	0.001	1.71-8.5	3.8

*)Fisher's exact test

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Acknowledgement