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ORIGINAL ARTICLE

Pregnancy complicated by Myasthenia gravis – twelve years experience

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Abstract

OBJECTIVE: The aim of the study was to evaluate the effect of Myasthenia gravis (MG) on the course of pregnancy, labor and delivery, and the condition of neonate.

DESIGN AND SETTINGS: Retrospective chart review of pregnant patients with MG hospitalized in tertiary care center over 12 year period was performed. Course of MG before and during pregnancy, mode of delivery, and condition of the newborn were analyzed.

RESULTS: There was 42 913 deliveries in the Polish Mother's Research Institute in Lodz during analyzed period. Thirteen patients with MG were identified, giving the incidence of 3/10 000 live births. Mean age of the patients was 28 years, range 18–36 years. Average time since diagnosis was 9 years. Eleven women with MG delivered at term (one twin pregnancy), and two babies were born prematurely. In seven patients pregnancy was ended via normal spontaneous vaginal delivery (NSVD), one was forceps extraction, four patients had elective Cesarean Section (CS), and two had emergency CS. Indications for CS were purely obstetrical. Spontaneous vaginal deliveries were speedy. None of the patients had exacerbation of MG during current pregnancy. Mean birth weight of the newborns was 3014,3 g, range 1730 g to 3700 g. Mean Apgar score was 8,7 at 1 minute and 8,9 at 5 minutes. Only one neonate (second twin) developed Transient Neonatal Myasthenia Gravis (TNMG).

CONCLUSIONS: Myasthenia gravis did not have significant effect on the course of pregnancy or mode of delivery. In the twin pregnancies it is possible that only one twin will present with the symptoms of TNMG.

Abbreviations:

AMG – arthrogryposis multiplex congenital
CNS – central nervous system
CSF – cerebro –spinal fluid
CS – cesarean section
IUGR – intrauterine growth restriction
MG – Myasthenia gravis
NSVD – normal spontaneous vaginal delivery
OB/GYN – obstetrics/gynecology
SNMG – seronegative myasthenia gravis
TNMG – transient neonatal myasthenia gravis

Introduction

Myasthenia gravis (MG) is a chronic neurological disease characterized by an abnormal neuromuscular transmission affecting mainly the nicotinic acetylcholine receptors, and caused by the specific IgG antibodies directed against the alfa-subunit of the nicotinic receptor.[36, 37] Clinically the disease presents as a weakness and fatigue of the striated muscles abating after longer or shorter period of rest. Ocular symptoms are the most common. Patients are complaining of double vision, decreased visual acuity, dropping eyelids. With involvement of bulbar muscles chewing, swallowing, and also speech might be impaired. Progressive disease process may affect the function of the upper and lower extremities resulting in difficulties walking and performing simple daily tasks. If the respiratory muscles are affected patient will present with respiratory problems [15].

Material and Methods

Medical records of thirteen pregnant patients with myasthenia gravis hospitalized between January 1, 1992 and December 31, 2004 in the Department of Perinatal Medicine of the Polish Mother's Research Institute in Lodz were analyzed retrospectively. The following aspects of the course of pregnancy, labor and delivery, and newborn's condition were reviewed and evaluated:

- duration, type, course, and management of the myasthenia gravis
- course of pregnancy including the number of hospital admissions
- coexisting medical conditions
- mode of delivery
- course of delivery
- condition of the newborn immediately after birth and during postnatal period

Results

There was 42 913 deliveries in the Polish Mother's Research Institute in Lodz during analyzed period. Our institution is a level III referral center for the complicated pregnancies, and in most cases pregnant patients with myasthenia gravis from the macro region of Lodz are being followed in our OB/GYN clinics. In 65, 7% of cases women delivered via normal spontaneous vaginal delivery (NSVD), 4,3% of deliveries were for-

Table1: Number of deliveries and mode of delivery

Number of deliveries	Spontaneous vaginal delivery	Forceps assisted	Breech presentation with manual maneuvers	*Cesarean section*
42.913	28.209	1.841	534	12,329
% of total number of deliveries	65,75%	4,3%	1,2%	28,75%

Table 2: Clinical characteristics of the pregnant patients included in the study.

Number	Age	G	P	Week of pregnancy	Years since diagnosis	Thymec-tomy	Medica-tions	Number of hospital admissions	*Thyroid autoimmune diseases*
1	31	1	1	40	20	No	Yes	3	No
2	36	1	1	38	18	No	Yes	3	No
3	35	3	2	38	10	No	Yes	2	Yes
4	27	1	1	40	8	Yes	Yes	0	Yes
5	27	1	1	40	8	No	Yes	1	No
6	22	2	2	39	10	Yes	Yes	1	No
7	25	1	1	34	13	Yes	Yes	0	No
8	30	3	3	38	9	Yes	Yes	1	No
9	18	1	1	38	3	No	Yes	0	No
10	30	1	1	40	3	Yes	No	1	No
11	37	1	1	32	10	No	Yes	2	No
12	21	1	1	40	4	No	Yes	2	No
13	25	1	1	38	6	Yes	No	2	No
Mean	28			38,07	9,38				

G – gravida (which pregnancy)
P – para (which delivery)

Table 3: Mode of delivery in the patients with myasthenia gravis.

Number	NSVD	Vaginal, forceps assisted	Cesarean Section	*Indications for Cesarean Section*
1	Yes			
2			Yes	Transverse lie of the second twin
3	Yes			
4	Yes			
5			Yes	Fetal distress
6		Yes		Fetal distress
7			Yes	Intrauterine Growth Restriction, oligohydramnios, worsening fetal condition.
8			Yes	Incomplete breechpresentation
9	Yes			
10	Yes			
11	Yes			
12			Yes	Fetal distress
13			Yes	Incomplete breech presentation.

Table 4: Duration of the individual stages of labor, blood loss, use of stimulation of labor in the pregnant patients with myasthenia gravis.

Number	I stage (minutes)	II stage (minutes)	III stage (minutes)	*Blood loss (in ml)*	Uterine contractions stimulation in the I stage of labor
1	190	35	5	200	Yes
3	300	10	5	300	Yes
4	480	15	5	300	Yes
6	240	10	10	300	No
9	480	30	10	350	Yes
10	280	10	5	250	No
11	350	15	30	300	No
Mean	331,43	17,86	10	285,71	

ceps assisted, in 1,2% of cases manual maneuvers were applied, and in 28,7% cesarean section was performed *(Table 1)*. In the analyzed group of pregnant patients incidence of myasthenia gravis was 3/10 000 (0,03%).

Since there is no standard recommendations in regard to the management of the pregnant patients with myasthenia gravis all the epidemiological indices related to that problem should be regarded as a description of the particular group, and not as a trend in the general population.

All women in the analyzed group had the generalized type of Myasthenia gravis. Age of the patients was (mean, range) 28 years, 18–36 years. Time since diagnosis of Myasthenia gravis was on average 9 years. In two patients the disease was diagnosed for more than 15 years (14,3%), in four cases the diagnosis was made 10–15 years before current pregnancy (28,6%), four patients had the diagnosis for 5–10 years (28,6%), and three pregnant women were diagnosed less than 5 years before this pregnancy (21,4%). Six patients in the group (64,3%) had undergone the thymectomy some time in the past. Twelve patients (85,7%) declared regularly taking acetylcholinesteraze inhibitors, and two patients (14,3%) admitted taking the medications sporadically. Two patients (14,3%) had coexisting autoimmune diseases of the thyroid *(Table 2)*.

In the studied group eleven patients (85,7%) delivered at term, including one twin pregnancy. Two women delivered prematurely at 32 and 34 weeks respectively.

All patients were followed by the obstetrician and neurologist in the level III referral center.

In the analyzed group of patients pregnancy did not cause exacerbation of the myasthenia gravis. However, ten out of thirteen patients required hospital admission in the current pregnancy. Two patients (14,3%) were hospitalized three times, four (28,6%) twice, and another four patients (28,6%) were admitted once to the hospital during the course of current pregnancy. Indications for hospital admissions were obstetrical, not related to myasthenia gravis.

Nine patients (71,4%) were qualified for the NSVD, and elective Cesarean Section was performed in four patients (28,6%). Out of the nine patients qualified for NSVD one had forceps assisted delivery, and two had Cesarean Section. In all three cases fetal distress was the indication for the intervention. In five patients (37,5%) with arrested progress of the first stage of labor intravenous infusion of Oxytocin (5j/500 ml) was used to stimulate the uterine contractions.

Indications for four elective CC were purely obstetrical; incomplete breech presentation in two cases, transverse lie of the second twin in one case, and severe

Table 5: Characteristics of the newborns born to the mothers with Myasthenia gravis.

No	Weeks of pregnancy	Birth weight	First minute Apgar score	Five minutes Apgar score	Infections	Transient myasthenia	Prolonged hospitalization	*Other complications*
1	40	3500	10	10	No	No	No	
2	38	2500	8	9	No	No	No	
3	38	3100	9	9	No	No	No	Intrventricular Hemorrhage Grade II
4	38	3700	9	9	No	No	No	
5	40	3550	9	9	No	No	No	
6	39	3350	8	9	No	No	No	
7	39	3550	8	9	No	No	No	
8	38	2550 (Twin I)	8	9	No	No	No	
9	38	2400 (Twin II)	7	7	Yes	Yes	Yes	Neuroinfection
10	39	3000	9	9	No	No	No	
11	40	3270	9	9	No	No	No	
12	34	1730	8	8	Yes	No	Yes	Intraventricular Hemorrhage Grade II
13	40	2900	9	9	No	Yes	No	
14	38	3100	9	9	No	No	No	
	Mean	3014,3	8,57	8,93				
	P		0,105589					

IUGR with oligohydramnios, abnormal Doppler flow in the umbilical vessels and worsening fetal condition (Bishop index 5) in one patient. Indications for the elective CS were in accordance with the standard obstetrical practice in the Polish Mother's Research Institute at the time the study was conducted. Overall six patients (42,9%) with myasthenia gravis delivered via CS *(Table 3)*.

Spontaneous vaginal deliveries were speedy. The mean duration of individual stages of labor in the patients with myasthenia gravis was shorter than the same stages in the patients with non complicated deliveries. I stage lasted (mean time) less than six hours, II less than 20 minutes, and III 10 minutes *(Table 4)*.

Dynamic contractions of the uterus had a positive effect on the course of labor, and also contributed to the small blood loss associated with labor, which on average was 285,7 ml. The amount of blood loss was estimated by the experienced obstetrician. None of the women had worsening of the hemoglobin/hematocrit secondary to blood loss, and none required blood/blood products transfusions, or medications stimulating erythropoiesis.

Birth weight of the newborns was (mean, range) 3014,3 g, 1730g to 3700 g. The birth weight was appropriate for gestational age in all but one neonate (born prematurely at 34 weeks of gestation). Mean Apgar score was 8,7 and 8,9 points respectively at 1 and 5 minutes. Condition of thirteen neonates (93,3%) was described as good (Apgar score more than 7 points at 1 and 5 minutes of life). Only one patient had Apgar score 7 at 1 and 5 minutes, and his condition was evaluated as average *(Table 5)*.

The discrepancy between the number of deliveries (13), and number of neonates (14) comes from the fact that one twin pregnancy was analyzed. Second twin was a male, with birth weight 2400 g, received Apgar score 7, and had signs of congenital infection. In the early postnatal period that patient developed symptoms of Transient Neonatal Myasthenia Gravis, and required treatment with Mestinon. On the third day of life patient presented with seizure, episodes of apnea, profuse sweating, excessive salivation, and myosis. He eventually was intubated and transferred to the Neonatal Intensive Care Unit (NICU). In the NICU patient required mechanical ventilation, blood pressure supporting medications, and wide spectrum antibiotics. Until five days after discontinuation of Mestinon patient had decreased threshold for seizure. In attempt to decrease the concentration of the circulating antibodies directed against the cholinergic receptor exchange transfusion was performed. Procedure was carried out without complications, and the patient's condition improved significantly afterwards.

On the tenth day of life patient was successfully extubated. Later on patient was transferred to the ward specializing in the infectious diseases for further treatment of the central nervous system (CNS) infection confirmed by the positive culture of the cerebrospinal fluid (CSF).

There were no further episodes of TNMG observed during patient's hospital stay.

Our relatively small study group, only fourteen pregnant women with Myasthenia gravis, does not allow for drawing unequivocal conclusions, or making recommendations for the management of pregnancies complicated by that disease. However, the problem is very important, and more research is needed preferably well planned multi center trial.

Discussion

The incidence of Myasthenia gravis in the general population is 1/10 000 to 1/50 000, and it differs for different age groups [11, 29, 32] Higher than in the general population incidence of myasthenia in the group of pregnant patients analyzed in our study (3/10 000) can be explained by the fact that Polish Mother's Health Research Institute is the level III perinatal referral center, accepting patients with complicated pregnancies from the whole region of Lodz. Naturally it is not representative of the whole population, not even the population of women of childbearing age (18–30 years of age) which has the incidence of myasthenia four times higher than the general population [6, 21]. There is no definite association between Myasthenia gravis and infertility, spontaneous abortions, or preterm delivery. Even though, Myasthenia gravis is not a frequently encountered disease in the pregnant patients, because medications used to treat the mother as well as maternal antibodies directed against the cholinergic receptor can potentially cross the placenta, and affect the developing fetus, it remains a very important problem not only for the neurologists, but also for obstetricians and neonatologists [1, 8, 24, 27].

Patient with MG may have other coexisting autoimmune disorders [5, 25, 38]. Pregnant women with MG in our group are older than mean for the population, and high percentage of them are primiparous. Most likely they are planning their pregnancy more carefully being aware of all the possible complications [22].

Most of the investigators report that in 1/3 of the cases pregnancy will exacerbate MG, but overall the course of MG during pregnancy is very unpredictable [11, 17, 20, 22, 28]. In our series none of the pregnant patients suffered exacerbations during the course of pregnancy. Similar results were reported by other investigators [9]. Several factors might have contributed to such good outcome in our study. First, in all patients MG was well controlled before pregnancy. Second, since MG can cause serious complications in the mother and the baby all pregnant patients with MG in our institution were treated as high risk pregnancies, and managed by the team of specialists including obstetrician, and neurologist. Such close supervision could have resulted in a better outcome.

High percentage of patients delivering via NSVD suggests that in the absence of other contraindications pregnant women with MG should be given a chance of vaginal delivery [11].

In none of the patients in our study delivery was prolonged, and it is in agreement with reports of others. Myasthenia gravis does not affect the function of the smooth muscles of the uterus [10].

In all cases when operative procedures were necessary to complete the delivery the indications were obstetrical, not related to MG. Similar are reports in the literature [10].

Percentage of Cesarean Sections (CS) was higher in the patients with MG when compared with the mean for the population (42,9% vs. 28,75%), but that tendency was related to higher number of elective CS performed in the analyzed group of pregnant patients with MG.

TNMG is reported in 12–20% of newborns born to the mothers with Myasthenia gravis [4, 6, 17–19]. There are two clinical forms of TNMG typical (71%), and atypical (29%). In typical form patient usually presents with poor sucking, and generalized hypotonia. Patients with atypical form are born with arthrogryposis multiplex congenital (AMC)[19, 23]. There is no correlation between the severity of maternal MG during pregnancy, presence of antibodies in the mother's serum, and severity of TNMG [4, 13, 14, 16, 17, 23, 30, 31]. Cases of newborns with symptoms of TNMG born to the mothers with neither past not present evidence of presence of MG have been described in the literature.[2, 35] Most commonly newborns develop the TNMG within first 24 hrs of life [19]. Onset of TNMG beyond 3 days of life has not been reported in the literature. In 90% of the patients complete recovery is expected by 2 months of age, and remaining 10% should become symptoms free by 4 months of age [3, 12, 14, 19, 23]. Thymectomy and/or treatment of the mother with medications alleviates the symptoms of TNMG in the neonate [7, 11, 33]. Newborns with the TNMG are a huge clinical challenge for the neonatologist. Most commonly they present with difficulties sucking, swallowing, ptosis, ophtalmoparesis, weak cry, mild respiratory distress. In most serious cases respiratory distress requiring assisted ventilation may occur. Mortality associated with TNMG is usually secondary to aspiration and/or respiratory failure, and is estimated to be around 11%.

In majority of the patients TNMG is caused by the effect of the maternal antibodies directed against the nicotinic acetylcholine receptor transferred to the fetal circulation. However, there are reports in the literature describing the neonates with so called Seronegative Myasthenia Gravis (SNMG), in which acetylcholine receptor antibodies titer determined using radioimmunoassay (RIA) was negative[37].

In our series TNMG was a rare complication. Only one newborn developed the symptoms. Interestingly it was one of the twins. Similar case was described in the literature [26]. Twins in our study were dichorionic-diamniotic, so metabolically and immunologically two different organisms. It is possible that even though both twins were growing in the same environment in utero, genetic factors prevented the development of TNMG in one of the twins. It would be interesting to see the outcome of monochorionic-monoamniotic twin pregnancy complicated by MG, in which at least theoretically the influence of genetics should be minimal. However, taking into consideration that feto – maternal exchange in such pregnancy does not have to be identical for both fetuses the concordance rate for TNMG probably would not be 100% either. No case of monochorionic-monoamniotic twins in which one or both babies would develop TNMG have been described in the literature until now. Treatment of TNMG is usually pyridostygmin (mestinon), and some times other measures like exchange transfusion or intravenous infusion of immunoglobulin are necessary [34]. Our

patient improved significantly after exchange transfusion was performed.

Conclusions

Pregnant women with Myasthenia gravis should be cared for in the tertiary care center. Interdisciplinary team of specialists responsible for the management of such high risk pregnancy should include obstetrician and neurologist.

In the group of patients analyzed in our study Myasthenia gravis did not have significant effect on the course of pregnancy. Mode of delivery was determined by the obstetrical factors, and was not significantly influenced by the presence of disease in the pregnant women.

Transient Neonatal Myasthenia Gravis, very serious complication of the maternal MG, may develop in the early neonatal period in some of the newborns born to the mother with MG. In the twin pregnancies it is possible that only one twin will present with the symptoms of TNMG.

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