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Case Report

Pregnancy with Myasthenia Gravis

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ARTICLE INFO

Submitted : November 2019

Accepted : December 2019

Published : January 2020

Keywords:

Pregnancy, Myasthenia Gravis

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ABSTRACT

Myasthenia Gravis (MG) is a serious autoimmune disease, but now can be treated. Symptoms include weakness and fatigue in voluntary muscles caused by an autoantibody reaction to nicotinic acetylcholine receptor (AChR) at the post synapse of the neuromuscular junction. Pregnancy can affect autoimmune diseases so that pregnancy can aggravate MG disease. On the other hand it is also reported that pregnancy does not affect and can even improve MG disease. In this article, We report a 27-year-old woman who was diagnosed with myasthenia gravis that having a pregnancy. Initially she had no problems with pregnancy. Patients underwent pregnancy by taking the drug Mestinon four times daily and roborant. But entering the 33rd-34th week, the examination results showed that the pregnancy experienced oligohydramnios and Intrauterine Growth Retardation (IUGR), it was probably caused by malnutrition. Then we decided to end the patient's pregnancy with a Caesarean section. The operation went well, born to a baby boy / 2450grams / Apgar Score 5-7. Observation for one week the mother's condition continued to improve. Diplopia and weaknesses also improve. Likewise the baby showed a healthy condition. The patient was discharged while still taking MG drugs that had been previously consumed. This case report showed that pregnancy worsened MG disease, but MG did not affect pregnancy.



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INTRODUCTION

Myasthenia Gravis (MG) is a serious autoimmune disease, but now can be treated. Symptoms include weakness and fatigue in voluntary muscles caused by an autoantibody reaction to the nicotinic acetylcholine receptor (AChR) at the post synapse of the neuromuscular junction. The neuromuscular junction damage was first shown by Engel and colleagues in an ultrastructure study of motor endplate (Gilhus, 2016).

Pregnancy can affect autoimmune diseases so that pregnancy can aggravate MG disease. On the other hand, it is also reported that pregnancy does not affect and can even improve MG disease. A study states that 1/3 cases of pregnancy will worsen, 1/3 does not affect, and the remaining 1/3 will even improve on the state of MG disease (Téllez-Zenteno, Hernández-Ronquillo, Salinas, Estanol, & da Silva, 2004).

Myasthenia crisis can occur and affect the condition of the fetus in the womb. This case reports a pregnant woman suffering from MG. For diagnosis, physical, laboratory and other supporting examinations are carried out. Furthermore, comprehensive management is carried out. Monitoring the state of the fetus while in the womb is very important, because MG can affect the growth and development of the fetus while in the womb (Hamel & Ciafaloni, 2018).

The patient was then treated with drugs for MG. Pregnancy in these patients ended with a Caesarean section at 36 weeks of gestation not because of maternal indications, but rather because of fetal indications where serial ultrasound examination began to show fetal growth disturbance accompanied by reduced amniotic fluid despite intrauterine resuscitation. The mother's condition after surgery improved. The baby was monitored after delivery, and there are no symptoms of MG. Mother and baby were sent home in

CASE REPORT

Anamnesis

A patient Mrs. M, 27 years old, came to the outpatient clinic to control pregnancy. She had three months pregnant and this was her first pregnancy. Previously, the patient controlled in Jakarta and had been diagnosed with myasthenia gravis. For the time being, she wanted to go home to give birth in her hometown. She did not have Diabetes mellitus, asthma, hypertension, heart disease, and allergy.

Patients had weakness in the muscles since 1 year ago relapsing in both hands and feet, and could not walk since four months ago. The eyes felt heavy and partially closing. The eye closed more as the weakness in the limbs worsened. The vision appeared double, sometimes appeared vertically blurred. Other complaints were not obtained. In the past, she consumed drug Mestinon twice a day.

Physical examination

GCS: 456, Vital sign: within normal limit

Obstetric examination :

His : -

USG : Breech / Single / DJJ +

BPD : 36

CRL : 74

DJJ : + doppler

V/v : Fluxus -

Neurological examination :

Diplopia

Motoric 3 3 4 5 5 5 5 4 3 3

hypotonia

3 3 4 5 5 5 5 4 3 3

Vocal test (+)

Laboratorium Examination :

Hb : 12,2 g/dl

Leucocyte : 8870/ml

Thrombocyte : 204.000/ml



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Creatinine serum : 0,4 mg/dl (<1,2)
 Potassium : 4,1 meq/l (3,8-5,0)
 Sodium : 136 meq/l (135-144)
 SGOT : 23 U/l (<38)
 SGPT : 15 U/l (<41)
 EMG : Myasthenia Gravis

Assessment

GI P₀₋₀ 16/17 weeks pregnant + Myasthenia Gravis

Treatment

Mestinon 4 x 1, Roboransia 1 x 1

Tabel 1. Continued Observation

	13 th December 2018	15 th December 2018	16 th December 2018
S	contraction-, fetal movement + GCS 456, Vital sign: normal Obstetric examination : DJJ + 13-12-13 USG: H / Single / DJJ + BPD: 87,3 ~33/34 FL: 65,8 ~33/34 mmm Placenta corpus anterior /II/ AFI 9,7 ml Doppler A. umbilicalis : PI : 1,36 RI : 0,71 Non Stress Test : Baseline 130-140 Variability 2-4 FAD reactive Neurologic examination Diplopia Strength 33455 55433 33455 55433	contraction-, fetal movement + GCS 456, Vital sign: normal Obstetric examination : DJJ + 13-12-13 USG: H/ Single / DJJ + BPD: 87,3 ~ 33/34 FL: 65,8 ~ 33/34 mmm Placenta corpus anterior/II/ AFI 9,7 ml Doppler A. umbilicalis : PI : 1,36 RI : 0,71 Non Stress Test : Baseline 130-140 Variability 2-4 FAD reactive Neurologic examination Diplopia Strength 33455 55433 33455 55433	<i>Low Segmen Caesar Section + Tubectomy Pomeroy Bilateral</i> General anesthesia: Phentanyl 50 mg Morphine 2 mg Recoval 110 mg Baby boy / 2450gr / AS 5-7 20 December 2018 Motoric: 44555 55544 44555 55544
A	GI P ₀₋₀ 33/34 weeks + Oligohydramnion+ MG	GI P ₀₋₀ 33/34 weeks + Oligohydramnion+ IUGR + MG	
P	Intrauterine resuscitation USG repeated 2 days	Plan Sectio Caesarian	

Furthermore, the patient was treated for one week. The patient's condition was good. Diplopia complaints and weaknesses improved. Then the patient was discharged by continuing Mestinon 4 x 1 therapy and Methyl Prednisolone 60mg-0-0. After underwent observation, three days later, the baby was also discharged in a good condition.



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LITERATURE REVIEW

MYASTHENIA GRAVIS

Myasthenia Gravis (MG) is an autoimmune disease with symptoms of weakness and fatigue in voluntary muscles caused by an autoantibody reaction to acetylcholine receptors (AChR) at post synapses at the neuromuscular junction. MG is the most common neuromuscular junction disorder. The incidence of MG in the United Kingdom is 15 / 100,000 population with an incidence of 1.1 / 100,000 population per year (Hill, 2003), while in Virginia 1.5 / 10,000 population. MG can attack all ages but is most abundant in the 3rd decade and decades 6 and 7 (Thanvi, 2004).

The neuromuscular junction damage was first shown by Engel and colleagues in an ultrastructure study of motor endplate. The use of neostigmine, an oral anti-cholinesterase for patients with MG was first performed in 1935. Lindstrom and colleagues showed antibodies to the AChR protein in approximately 87% of MG patients. Recently found antibodies that bind to muscle specific protein kinase (MuSK), a specific protein present in muscles that can be found in patients with MG where no antibodies to AChR are found. The molecular structure of AChR and the presence of receptors in human muscles can now be studied (Thanvi, 2004). In the presence of antibodies that bind to AChR, it will cause a blockade of AChR so that it will reduce the amount of AChR that can bind to acetylcholine released from terminal nerve presynaptic (Gilhus, 2016).

The clinical picture of MG patients is a history of muscle weakness or muscle fatigue that occurs during activity and will improve with rest. Complaints will increase at dusk. Several factors will aggravate complaints, including exercise, hot temperatures, infections, emotions, some drugs (aminoglycosides,

phenytoin, some local anesthetic drugs), surgery, menstruation, and pregnancy. Some of the muscles that are frequently affected by MG are the superior palpebrae levator muscle, extraocular muscles, lower movable muscles, facial muscles, and neck extensors. Ptosis due to superior palpebrae muscle weakness is usually only partial and unilateral (Gilhus, 2016).

Another complaint is the difficulty in closing the eyes, this is due to the weakness of the orbicularis oculi muscle. When the facial muscles are affected, the face will look as without expression. The mouth will always appear open and maybe the patient needs to support his jaw with a finger. The loss of sound is due to the weakness of the larynx. Voice while talking will increasingly weaker (Schwendimann, Burton, & Minagar, 2005).

The progression of muscle weakness in MG sufferers usually occurs from the top down: face → bulbar → trunkal → locomotor. Weaknesses of intercostal muscles and diaphragms can cause breathing problems when on the move even at rest. The occurrence of orthopnoea but will heal quickly on standing, and the paradoxical occurrence of the diaphragm is an important clinical sign of respiratory muscle disorders. Respiratory problems can occur suddenly in a few hours so that patients need to be monitored closely by monitoring their vital signs (Schwendimann et al., 2005).

Etiopathology Myasthenia Gravis

It is now well known that MG is a disorder caused by antibodies at the neuromuscular junction. Several explanations explain that MG is caused by an antibody process: (Thanvi, 2004)

1. Antibodies to AChR are found in 90% of patients with general MG
2. anti-AChR antibodies are found in transient MG in neonates, and their levels will decrease during the healing



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3. Passive transfer of IgG from patients with MG in mice will cause the same disease as MG.
4. Plasmapheresis will reduce the level of AChR antibodies so that it will improve the condition of patients with MG.
5. Antibodies bind to AChR at the neuromuscular junction.
6. In animal studies, MG can be caused by immunization.

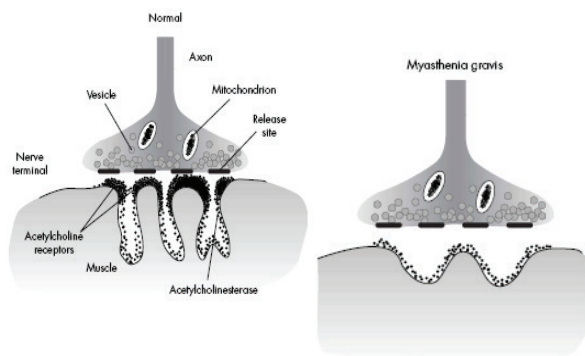


Figure 1. Neuromuscular junction normal and in MG patient (Thanvi, 2004)

Damage to AChR by antibodies caused by the mechanism:

1. Antibodies will bind to AChR with the result cause AChR degeneration of muscle cells.
2. Antibodies will block by binding to AChR
3. Complement will cause junctional fold damage from the postsynaptic membrane.

AChR antibody levels in patients with MG are not related to the severity of the disease. The gravity of MG depends on the functional activity of the antibody.

Myasthenia And Pregnancy

MG can be triggered during pregnancy or after delivery. Pregnant women with MG have several challenges in terms of treatment, so special and coordinated treatment is needed between neurologists, obstetricians, and neonatologists

(Téllez-Zenteno et al., 2004).

Hormones affect autoimmune diseases. Estrogen and progesterone work by suppressing macrophages that will reduce the production of TNF- α and IL-12. High estrogen will also cause the production of IL-10. In experimental animals, estradiol (E2) will cause impaired tolerance in B cells (Yi, Guptill, Stathopoulos, Nowak, & O'Connor, 2018).

Pregnancy where hyperestrogens occur is related to the cytokine profile produced by Th2, this is important to maintain the tolerance of the mother to the fetus she is carrying. This will be different if the mother suffers from autoimmune diseases, for example in rheumatoid arthritis and multiple sclerosis, where Th1 is more dominant, the autoimmune disease will improve, but this is different for example in patients with SLE where the role of Th2 is greater, then pregnancy with conditions that are more hyperestrogens will cause lupus shock (Téllez-Zenteno et al., 2004).

Influence Of Pregnancy In Myasthenia Gravis

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The Effect Of Myasthenia Gravis In Pregnancy

In the study, data were obtained that the effect of MG on pregnancy and childbirth was the occurrence of premature rupture of membranes and the use of obstetric measures (use of forceps and caesarean sections) was more common in patients with MG (Téllez-Zenteno et al., 2004). In pregnant women with MG the incidence of premature rupture of membranes is three times more than pregnant women who do not suffer from MG. This is thought to be possible because of treatment using corticosteroids (Bansal, Goyal, & Modi, 2018).

The Effect Of Myasthenia On New Fetal And Babies

The complication of pregnancy with MG in the fetus is the occurrence of arthrogryposis multiplex congenita (AMC) which is characterized by the occurrence of multiple contractures in the joints while the fetus is in the womb. Some cases occur due to genetic factors, but AMC is usually a complication of pregnancy in patients with MG that is thought to be caused by antibodies in the maternal circulation (Hamel & Ciafaloni, 2018). Multiple contractures occur because antibodies from the mother can penetrate the placental barrier and will attack AChR from the fetus, which will cause disruption in the movement of the fetus in the womb and will result in contractures of the fetal joints

(Phillips & Vincent, 2016).

Zenteno reported an incidence of 21% occurring transient neonatal myasthenia gravis (TNMG) in newborns born to mothers suffering from MG. In this report 67% of newborns experience TNMG in the first few hours after birth and 78% experience TNMG in the first 24 hours. The occurrence of TNMG after 3 days was never reported. In MG associated with AMC, death often occurs in newborns. The mechanism that allows the occurrence of TNMG is antibodies from the mother through the placental barrier with the result of inhibition of AChR, causing paralysis in the fetus. Clinical features of TNMG look like overall muscle weakness and inadequate sucking from infants (Téllez-Zenteno et al., 2004). The severity of the mother's disease is not related to the severity of the baby TNMG it contains, TNMG can also occur in mothers with MG in the healing phase (Hamel & Ciafaloni, 2018).

Treatment Of Myasthenia Gravis In Pregnancy

Current MG treatment has very high effectiveness. Before 1958, the mortality rate was around 30% with current treatments. At present, with adequate treatment the mortality rate can be reduced to 0%. MG treatments include Acetylcholinesterase inhibitors, Corticosteroids, Immunosuppressants, Plasmapheresis, Intravenous immunoglobulins, Thymectomy. The use of drugs in MG women who are pregnant or want to become pregnant are given individually based on the severity of the disease and the distribution of muscle weakness (Bansal et al., 2018).

MG treatment can be divided into three stages, namely: (1) initial treatment, which usually uses acetylcholinesterase inhibitors. But these drugs are usually inadequate to control this disease, so additional therapy is needed. (2) Usually, direct treatment of immunological reactions



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needs to be done, starting with a thymectomy and the use of high doses of corticosteroids. (3) For long-term treatment, steroid-sparing medications need to be added at the time of steroid tapering. Short-term treatment with intravenous immunoglobulin or plasmapheresis may be effective in the early stages of treatment. (Thanvi, 2004) Plasmapheresis is safe for use in pregnant MG patients (Téllez-Zenteno et al., 2004). But in theory, plasmapheresis will increase the occurrence of preterm labor due to the loss of hormones in the circulation at the time of plasmapheresis (Bansal et al., 2018).

MG treatment using anticholinesterases and steroids did not have a significant relationship with the risk of fetal abnormalities (Téllez-Zenteno et al., 2004). Corticosteroid treatment is very effective in most MG patients and can be an option for treatment in pregnant women where immunosuppression therapy is needed to treat MG that is getting worse during pregnancy. The use of high doses of corticosteroids may be associated with premature rupture of membranes (Waters, 2019). The drug commonly used is prednisone at a dose of 1 mg / kg per day, given as a one-time dose (Chaudhry, Vignarajah, & Koren, 2012).

Because of the serious side effects of long-term use of corticosteroids, steroid-sparing immunosuppression drugs have been developed, including azathioprine, cyclophosphamide, cyclosporine, methotrexate and new mycophenolate mofetil (Chaudhry et al., 2012). The use of immunosuppressants should be avoided during pregnancy because of its teratogenic effects (Waters, 2019). Safety of the use of intravenous immunoglobulin in MG patients who are pregnant until now there has been no report.

Thymectomy during pregnancy is out of place because with the expected effect the thymectomy is slow and increases the risk due to the surgical procedure. If there is an indication

that a thymectomy is performed, it should be done before being planned for pregnancy or after delivery (Chaudhry et al., 2012).

Labor

MG usually does not affect the first phase of labor, because MG does not affect smooth muscle (Chaudhry et al., 2012), but the abdominal striated muscles. Nevertheless obstetric complications are uncommon in patients with MG. If there is muscle weakness during labor, cholinesterase inhibitors can be given intravenously, because in oral administration we cannot estimate the absorption of the drug in the digestive tract. Neostigmine can be given at a dose of 1.5 mg intra-muscular or 0.5 mg intravenously (Téllez-Zenteno et al., 2004). Surgical action on patients with MG is an act that causes very heavy stress, therefore births with sectio caesarian measures are only performed in cases that are necessary only (Waters, 2019).

DISCUSSION

In this patient the clinical symptoms that appear were muscle weakness that began one year before the patient was pregnant. The weakness felt to get heavier, along with the duration of the activity. Also visible when the patient was talking for a long time the voice will get weaker. Ptosis was found in the eye. While investigations by anti-AChR antibody examination showed normal numbers, the possibility of the patient was MG sufferers from the seronegative group. Whereas the examination of anti-MuSK antibodies is still in the research discourse, there is no commercial kit yet. Another test performed was to use electrophysiology which supported the diagnosis of MG.

The effect of pregnancy on MG varies and cannot be predicted with certainty. Approximately 1/3 of myasthenia sufferers will improve with their pregnancy and 1/3 will worsen the condition



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of myasthenia during their pregnancy, while the rest do not change the state of myasthenia. Usually, the worsening of this disease occurs in the early trimester of pregnancy and rarely occurs in the third trimester of pregnancy (Riemersma et al., 1996). It is generally thought that pregnancy is associated with immunosuppression. With the onset of depression from leukocyte function it will lead to an improvement in the condition in patients with autoimmune diseases. But some autoimmune diseases will be aggravated by pregnancy (Téllez-Zenteno et al., 2004).

In this patient, it seems that the pregnancy was exacerbating MG, because it was obtained after delivery that clinical symptoms appear to be marked by ptosis and muscle weakness improves. In infants there appears to be no motor impairment where the baby was able to breathe and suck well.

The effect of MG on pregnancy and childbirth is the occurrence of premature rupture of membranes and the use of obstetric measures (use of forceps and caesarean sections). While the influence of MG on the fetus is the occurrence of arthrogryposis multiplex congenita (AMC) which is characterized by the occurrence of multiple contractures in the joints while the fetus is in the womb. Some cases occur due to genetic factors, but AMC is usually a complication of pregnancy in patients with MG that is thought to be caused by antibodies in the maternal circulation (Chaudhry et al., 2012).

In this patient, the pregnancy problem obtained was IUGR. However, this IUGR was most likely not related to MG, but rather was caused by a lack of nutrition of the patient during pregnancy because it was recognized by the patient that she was quite stressed and worried about this pregnancy so that her appetite was reduced.

After an indication of IUGR was found in this patient, intrauterine resuscitation was initially carried out, but with serial ultrasound apparently there was no improvement in the condition of the fetus so at the age of 36 weeks it was decided to terminate the pregnancy by Caesarean section.

CONCLUSION

During pregnancy, there are significant changes in hormonal conditions where it is known that hormonal factors are associated with the occurrence of autoimmune diseases. So pregnancy can affect autoimmune diseases. Pregnancy can worsen the state of autoimmune disease.

In this case report, it was found that the pregnancy made the MG disease worse. After birth, complain of motor weakness and diplopia improved. The MG does not seem to have an effect on the patient's pregnancy. Olygohidramnions in this patient seem to be caused by low intake.

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