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REVIEW ARTICLE

Management of myasthenia gravis in pregnancy

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Abstract

To a neurologist, pregnancy and delivery are major issues for patients with neuroimmunological diseases, including myasthenia gravis (MG). MG is an autoimmune disease caused by antibodies against the nicotinic acetylcholine receptor or other postsynaptic antigens, such as muscle-specific kinase or low-density lipoprotein receptor-related protein 4. In Japan, a nationwide survey in 2006 showed that 15 100 people, or 11.8 per 100 000 persons, had been diagnosed with MG. In women with MG who became pregnant, the disease symptoms worsened for 41%, whereas 30% showed no change, and 29% had remission of symptoms. Exacerbations occur in the first trimester and in the first 3 months postpartum. It is also important to watch for transient neonatal MG, which occurs in 10–30% of infants delivered by mothers with MG. It is critical to carefully monitor antimuscle-specific kinase antibody-positive patients with MG because of their greater risk for bulbar palsy. The present review discusses the effects of pregnancy on MG and the management of MG in pregnancy.

Introduction

Myasthenia gravis (MG) is an autoimmune disease that can occur at any age. It is twice as common in women than in men, and is most common in women during their third decade of life.[1] The prevalence of early onset MG (age <40 years) is nearly threefold higher in females than in males, whereas the prevalence of late-onset MG (age >50 years) is more prevalent in men than in women.[2] In Japan, the estimated number of patients with MG in 2006 was 15 100,[3] giving a prevalence of 11.8 per 100 000 persons, and the number of Japanese with a Certificate of Specified Rate and Intractable Disease in 2013 was 20 691.[4] MG is not a rare disease, and women with MG who are pregnant or delivering are routinely encountered. In terms of MG disease activity during pregnancy, exacerbation is reported in one-third of patients, with remission reported in another third and no change reported in the last third. Particular attention is required when women who are taking adrenal cortical steroids or immunosuppressant agents for MG become pregnant, because of concerns for the effects of the MG medications on the fetus. Infants born to mothers with MG are no different from those born to healthy mothers in terms of newborn weight or the risk of cesarean delivery. Pregnancy and delivery do not adversely affect the long-term prognosis of women with MG. Exacerbation of MG is observed in approximately 30% of patients in the first trimester of pregnancy and immediately after birth, so careful control is necessary during these periods.[5] Furthermore, women are vulnerable to hypotonic contractions when they become fatigued, and transient neonatal MG (TNMG) caused by transfer of maternal antibodies during the perinatal period is possible, making special care required.

Antenatal care of patients with MG who plan to become pregnant

When a patient with MG becomes pregnant, care is required to avoid exacerbation. Starting glucocorticoid therapy or withdrawing immunosuppressant therapy might cause transient worsening of MG.

All infections should be treated promptly. Djelmis et al. reported that pregnant MG patients with underlying infections have developed exacerbation of MG.[6]

An initial evaluation of pregnant patients with MG includes assessment of baseline motor strength, pulmonary function and electrocardiographs. Rare cases with focal myocardial necrosis have been recorded among patients with MG.[7]

Thyroid function tests should be carried out and evaluated. The rate of association with an autoimmune disease (primarily thyroid disease) among patients with MG is 13%.[8]

Management of thymectomy in a patient with MG who plans to become pregnant

Nearly 15% of persons with MG have thymoma.[9] Thymectomy is a standard treatment for MG patients with thymoma, but not for those with ocular type or muscle-specific kinase (MuSK) antibody-positive MG.[9] During pregnancy, patients with thymoma who have not undergone thymectomy present with a higher incidence of exacerbation than those who have undergone thymectomy.[10,11] Infants born to MG patients who have undergone thymectomy have less risk of developing neonatal MG.[12] Thus, thymectomy could be considered before conception or after delivery if a patient with MG plans to become pregnant in the future, but not during pregnancy.[13,14]

Effect of pregnancy on MG

Plauche et al. reported that exacerbation, remission, and no change in disease occurs in 41%, 29% and 30% of pregnant MG patients, respectively.[15] However, disease exacerbation tends to occur in the first trimester and in the puerperium.[5] Improvement of MG symptoms occurs during the second and third trimesters[16] as a result of the hormone-mediated immunosuppression known to occur in the normal progression of pregnancy.[15] Alpha-fetoprotein has been shown to inhibit binding of acetylcholine receptor (AChR) antibodies, and is at least partially responsible for the late pregnancy symptomatic improvement.[17] Postpartum exacerbations were noted in 30% of all patients with MG who had been pregnant.[18] Disease exacerbation and mortality are increased within the first year after MG is diagnosed; therefore, it is recommended that women of reproductive potential with MG avoid pregnancy for at least 1–2 years after initial disease diagnosis.[18]

Post-thymectomy pregnant patients have a lower incidence of disease exacerbation.[10,11] The data from the Medical Birth Registry of Norway reported that the infants of mothers with MG who had undergone thymectomy had a lower incidence of neonatal MG than those born to mothers without thymectomy.[12]

Because any pregnancy-associated infections, such as pyelonephritis, cystitis, mastitis and endometritis, exacerbate MG, these infections should be treated promptly.[6] Pregnancy does not worsen the long-term outcome of the disease.[15]

Effect of TNMG and MG on pregnancy

MG does not have any severe adverse effects on pregnancy.[17] No increase is observed for a mother with MG in the risks of spontaneous abortion, pre-eclampsia, cesarean section, fetal growth restriction or premature birth.[5] Overall, 10–30% of infants develop TNMG, because of the placental transfer of immunoglobulin G (IgG) anti-AChR antibodies in the second and third trimesters. Infants with TNMG typically develop symptoms, including respiratory problems, muscle weakness, feeble cry, poor sucking or ptosis, within 12 h to 4 days that persist from 2 weeks to several months after birth.[6,16] All infants delivered from MG mothers should be observed particularly carefully through the first week. These conditions recover spontaneously within 3–4 weeks after birth, because the antibodies transported from the mother are degraded.[16] The durations of maternal disease and medication for MG are not associated with the occurrence of neonatal MG.[19]

Management of pregnancy in MG patients with anti-MuSK antibodies

In patients with anti-AChR antibody-seronegative MG, approximately 40% have IgG antibodies against MuSK.[20] The test for anti-MuSK antibodies is negative in anti-AChR antibody-seropositive MG patients. Anti-MuSK antibody-positive patients often have prominent bulbar, neck, shoulder girdle and respiratory weakness. Anti-MuSK antibodies are more commonly found in women than in men.[21]

Anti-MuSK antibodies belong to IgG class 4, and their placental transfer is worse than that for anti-AChR antibodies, which are IgG1 and IgG3. The frequency of developing anti-MuSK antibodies in TNMG is low, but it is possible to transmit anti-MuSK antibodies from the umbilical cord to the newborn. When hydramnios or impaired swallowing in the newborn appears, it is necessary to treat early with plasma exchange.[22] One patient with anti-MuSK antibodies reported by Kansaki et al. had strong bulbar paralysis, and a potential existed for weakened treatment efficacy of plasma exchange

or for MG worsening postpartum.[22] Therefore, this patient was treated with tacrolimus after delivery and did not breastfeed. Furthermore, patients with anti-MuSK antibody-positive MG often have bulbar paralysis, giving rise to the possibility of developmental disorders in the infants because of malnutrition. Thus, the proactive use of enteral nutrients administered orally, or tube feeding, is also thought to be necessary. In postpartum treatment of patients with anti-MuSK antibody-positive MG, the effects of steroid pulse therapy tend to be transient and of shorter duration than those in MG patients positive for anti-AChR antibodies. Hence, in the former patients, prednisolone, primarily with immunosuppressant agents, is necessary for a certain period of time and in adequate amounts.[22] Pregnancy and birth in patients with anti-MuSK-antibody-positive MG share many commonalities with pregnancy and birth in patients with anti-AChR-antibody-positive MG, and in a risk of crisis, the selection of plasma exchange and the consideration of TNMG are the same in both.[23] However, management in these patient populations differs because of the bulbar paralysis that is characteristic of MG patients with anti-MuSK antibodies. This group of mothers and infants needs to be monitored especially carefully for nutritional deficiencies and hydramnios, and plasmapheresis should be carried out without delay.[22]

Additional studies in pregnant MG patients positive for anti-MuSK antibodies are required. Because maternal MG with anti-MuSK antibodies might be associated with early and more severe neonatal manifestations, infants delivered from these mothers require close observation.[22]

Delivery and anesthesia considerations

Vaginal delivery is recommended for women with MG.[17] MG does not affect the first stage of labor, because the uterus consists of smooth muscle, which is unaffected by the presence of AChR antibodies.[17] However, assistance in the form of forceps or vacuum extraction might be required in the second stage of labor, because striated muscles are involved during this stage, and these muscles are affected by AChR antibodies.[11] Operative vaginal delivery might reduce maternal fatigue and weakness. Cesarean section should be carried out only for obstetric indications, as surgery is stressful for women with MG.[12] Patients with MG should continue their usual medications, including oral steroids (>7.5 mg per day or >15 mg on alternate days), and should be given stress-dose parenteral hydrocortisone (100 mg t.i.d., i.v.) during labor.[24]

Pain relief during labor and delivery is not contraindicated. Epidural anesthesia is recommended during labor and delivery.[6,11] However, both general anesthesia and narcotics should generally be avoided because of their ability to synergistically potentiate AChR antibody effects.[14]

Medical management during pregnancy and breastfeeding

Anticholinesterase agents are the treatment of first choice for MG during pregnancy. Adrenal cortical steroids can be continued at the lowest possible doses. Generally, immunosuppressant agents are contraindicated during pregnancy, but tacrolimus and cyclosporine can be administered in cases where the stabilization of the disease in the mother takes precedence over the risks (Table 1). If there is a risk of crisis, plasmapheresis and intravenous immunoglobulin (IVIg) should be selected.[23]

Table 2 shows the medications to avoid during the perinatal period in women with MG.[14]

Acetylcholine esterase inhibitor (pyridostigmine)

Pyridostigmine (Food and Drug Administration [FDA] category B) is not expected to cross the placenta in significant amounts, and there have been no reports of fetal malformations.[25] This supports the safe use of pyridostigmine by women with MG during pregnancy. Breastfed infants of mothers taking pyridostigmine ingest <0.1% of the maternal dose, and the American Academy of Pediatrics considers pyridostigmine to be compatible with breastfeeding.[25] However, pyridostigmine dose adjustment is required in pregnancy as a result of increased renal clearance, expanded maternal blood volume, delayed gastric emptying and emesis.[26]

Corticosteroids

Maintenance steroids at the lowest possible dose are usually continued in pregnancy, because they cause minimal adverse effects in the mother and fetus.[25] Women with MG who are prescribed corticosteroids (FDA category B) must be informed before conception of the increased risk of oral clefts. Prednisolone is preferred, because it is metabolized by the placenta, and just 10% crosses into the fetal circulation at maternal doses of <20 mg.[27] Mothers receiving more than 7.5 mg prednisolone per day or 15 mg on

Table 1 Safety of drugs used in pregnancy and breastfeeding

Drug	FDA pregnancy risk category	Transplacental passage	Human teratogenicity	Breastfeeding allowed
Prednisone	B	Limited	Increase in oral clefts	Compatible with breastfeeding
Azathioprine	D	Yes	No	Avoid because of theoretical risk
Tacrolimus	C	Yes	Not reported	Breastfeeding probably possible
Cyclosporine	C	10–50% of maternal plasma concentration	No	No consensus, weigh risk/benefit
Mycophenolate mofetil	C	Yes	No	Avoid because of theoretical risk
Methotrexate	X	Methotrexate + polyglutamates	Yes	Avoid because of theoretical risk
Intravenous Immunoglobulin	C	Yes	No	Breastfeeding probably possible
Pyridostigmine	B	No	No	Yes

The United States Food and Drug Administration (FDA) pregnancy risk categories are as follows: A, no risk in controlled clinical studies in humans; B, human data reassuring, or when absent, animal studies show no risk; C, human data are lacking; animal studies show risk or are not done; D, positive evidence of risk, benefit may outweigh; X, contraindicated during pregnancy.

Table 2 Medications to avoid in women with myasthenia gravis

Curare, succinylcholine and related medications
Narcotic analgesics
Magnesium salts
Selected antibiotics
Aminoglycosides
Fluoroquinolones
Macrolides
Quinine, quinidine, procainamide Beta-blockers
Calcium channel blockers
D-penicillamine
Lithium

alternate days for more than 2 weeks before delivery should receive parenteral steroids to cover the stress of delivery. Steroids can be continued during breastfeeding, and there is evidence that neonatal adrenal suppression after exposure *in utero* or during breastfeeding does not occur.[24] We advise discarding breast milk for the first 4 h after ingestion of a dose of prednisolone ≥20 mg.

Calcineurin inhibitors (cyclosporine, tacrolimus)

Neither cyclosporine nor tacrolimus (FDA category C) is teratogenic.[28,29] However, there is an increased risk of gestational diabetes mellitus and hypertension in women taking tacrolimus. Therefore, screening with a glucose tolerance test is recommended at 28 weeks or sooner if there are other risk factors.[24] According to one case report, only 0.02% of the mother's dose of tacrolimus is transmitted to the breastfed infant.[30]

Cyclosporine is excreted in breast milk, and therapeutic levels have been reported in some breastfed infants.[31] The American Academy of Pediatrics has also stated that cyclosporine should not be administered to breastfeeding women.[32]

Immunosuppressants

Azathioprine

Azathioprine (FDA category D) has not been associated with increased rates of congenital abnormalities. However, there is evidence of possible intrauterine growth retardation and infants with low birthweight, as well as concern about immunological changes. Azathioprine and its metabolites have been found in milk, exposing the child to 0.1% of the maternal dose. The American Academy of Pediatrics does not recommend breastfeeding because of the theoretical risk of immunosuppression, carcinogenesis and growth restriction in the child.[33] However, both Ostensen et al. and Sau et al. reported that azathioprine is safe to use throughout pregnancy and breastfeeding.[33,34]

Mycophenolate mofetil

Recently, mycophenolate mofetil (FDA category C) was reclassified by the FDA as a class D drug, indicating that there is evidence of teratogenicity in human fetuses. It is associated with first trimester miscarriage, and structural malformations of the ears and jaw, cleft lip and palate, and hypoplastic fingers and toenails.[35,36]

Methotrexate

Methotrexate (FDA category X) is a folate inhibitor contraindicated in pregnancy and breastfeeding. If methotrexate is used in women considering pregnancy, it is recommended that a washout period of at least 3 months is allowed before conception.[24]

IVIg and plasmapheresis

IVIg (FDA category C; 400 mg/kg/day) is administered for the treatment of acute myasthenic exacerbation. IVIg during pregnancy for treatment of antiphospholipid antibody syndrome, autoimmune thrombocytopenic purpura and other autoimmune diseases is considered safe.[37,38] No data are available regarding fertility or breastfeeding, but harmful effects seem unlikely. IVIg can be used in pregnancy, and breastfeeding is allowed.[33]

Plasmapheresis can also be used in pregnancy to treat thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome.[39] Both IVIg and plasmapheresis are more likely to be effective in anti-MuSK antibody-positive MG patients.[21]

IVIg and plasmapheresis are reserved for cases where conventional therapy of MG has failed, and the development of respiratory failure or profound dysphagia and weakness threatens the mother and fetus.

Breastfeeding

Breastfeeding need not be contraindicated in mothers with MG if their disease is well controlled and there has been no indication of neonatal myasthenia. However, a mother with poorly controlled disease should consider not breastfeeding because of her increased likelihood of disease exacerbation resulting from the increased fatigue and effort associated with nursing. If the mother is treated with mycophenolate mofetil or methotrexate, nursing would be contraindicated.[14]

Contraception

MG does not reportedly decrease female fertility, and the relative hazards of pregnancy should be prospectively discussed with any women of reproductive potential who have the disease. Riemersma et al. reported exacerbation of MG symptoms during cyclic withdrawal from oral contraceptives.[40] Continuous hormonal contraception in the form of the pill, patch or ring without use of a hormone-free period might thus be a better contraceptive option for women with MG. Women with MG should be at no increased risk of complications with either barrier or intrauterine device contraception.[14,41]

Conclusion

In women with MG, disease exacerbation occurs during approximately 41% of pregnancies, remission in 29% and no change in 30%. Exacerbations occur in the first trimester and in the first 3 months postpartum.

There is no evidence that MG adversely affects pregnancy outcomes. Most of the medications used to control MG symptoms appear to be relatively safe during pregnancy, except for mycophenolate mofetil and methotrexate. We must consider the risk of transient neonatal MG, because the frequency is 10–20% in infants born of MG mothers. It is especially important to carefully monitor anti-MuSK antibody-positive MG patients, because bulbar palsy is a major concern.

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Conflict of interest

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