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Myasthenia gravis and pregnancy

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Autoimmune myasthenia gravis: brief overview

Acquired myasthenia gravis (MG) is an autoimmune disease in which autoantibodies against the acetylcholine receptor (AChR Abs) at the neuromuscular junction cause impaired neuromuscular transmission, leading to clinical weakness of skeletal muscles. Disease onset may occur at any age. Female incidence peaks in the third decade, whereas male incidence is greatest in the sixth and seventh decades of life. The mean age at onset is 28 in females and 42 in males. The ratio of female to male patients is 6:4. Juvenile MG, with onset before age 20, accounts for 10% to 15% of all patients who have MG. Patients who have onset before puberty are rare and show an equal sex ratio, whereas incidence in females increases during and after puberty.

Extrinsic ocular muscles are affected in the majority of patients and diplopia and ptosis frequently are the presenting symptoms. Weakness of limb muscles is fluctuating in nature, worsens with sustained exertion, and improves after rest. Injection of edrophonium, a short-acting acetylcholinesterase inhibitor, improves the muscle weakness and sometimes is used to confirm the diagnosis (Tensilon test). Acute exacerbations may be triggered by certain medications, intercurrent infections, surgery, general anesthesia, emotional stress, menses, pregnancy, and the postpartum state. Myasthenic crisis is a life-threatening exacerbation in which severe respiratory and bulbar weakness requires the use of mechanical ventilation. Patients who have MG frequently have other associated autoimmune disease, such as hypothyroidism, rheumatoid arthritis, pernicious anemia, vitiligo, polymyositis, or systemic lupus erythematosus.

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Clinical diagnosis is confirmed by the presence of serum AChR Abs in approximately 80% of patients who have the generalized form of MG and 50% of those who have MG limited to the ocular muscles (purely ocular MG). The recently discovered antibodies against the muscle-specific receptor tyrosine kinase are detected in approximately 70% of seronegative patients who have generalized MG [1].

Electrophysiologic testing can be useful in confirming the diagnosis of MG and in assessing its severity. Repetitive nerve stimulation testing at low frequency (3–5 Hz) is easily available and shows pathologic decrement of the compound muscle action potential in approximately 75% of patients who have MG. Single fiber electromyography (SFEMG) is a more sophisticated but less available test with a higher sensitivity in detecting abnormalities of neuromuscular transmission. Abnormal jitter and blocking are detected virtually in all patients who have MG if a clinically weak muscle is tested. Electrophysiologic testing is useful particularly in the diagnosis of seronegative patients.

Thymomas, mostly benign, are found in approximately 10% of myasthenic patients, are more frequent in patients over age 30, and are rare in juvenile MG. The thymus plays a key role in the pathologic breakdown of self-tolerance leading to MG, and thymic hyperplasia is found in 60% to 80% of myasthenic patients. Women of childbearing age who have MG have an enlarged thymus and circulating AChR Abs in most cases. Thymectomy is mandatory in patients who have thymomas and frequently is performed in patients who have onset of generalized MG before age 50.

Oral cholinesterase inhibitors, such as pyridostigmine (Mestinon) and, less frequently, neostigmine are used as symptomatic treatment and may be sufficient in managing the mildest cases. Corticosteroids, azathioprine (AZA), cyclosporine, and mycophenolate mofetil (MMF) are the immunosuppressant drugs (IS) most frequently used for long-term management of MG.

Plasmapheresis and intravenous immunoglobulin (IVIG) provide rapid onset improvement that persist for weeks. They are useful in the acute treatment of myasthenic exacerbations and crises, to optimize perioperative management before thymectomy or other major surgeries and, in managing severe cases, refractory to IS.

Issues related to the care of women who have myasthenia gravis

MG, like other autoimmune diseases, occurs commonly in women in their childbearing years. Female sex hormones are involved in thymic involution, have important effects on cell-mediated immunity, and generally enhance immune responsiveness. Myasthenic symptoms frequently worsen around the time of menses.

The onset of MG can be triggered during pregnancy or post partum. In pre-existing MG, exacerbations frequently are unpredictable and not unusual during pregnancy, labor, or the postpartum period. Although

pregnancy with an uneventful course and a good outcome frequently is possible in women who have MG, there are many challenging therapeutic decisions unique to myasthenic women planning for pregnancy. These require special clinical consideration and coordinated care between neurologists, obstetricians, and neonatologists. Management should be aimed at optimizing muscle strength in the mother, minimizing maternal risk of bulbar and respiratory exacerbation, protecting the fetus, and maintaining integrity of the pregnancy. Frequent emesis and changes in blood volume and renal clearance may interfere with absorption of oral medications and require frequent dosage adjustments. The growing fetus may restrict the diaphragm and compromise respiratory function. Breast-feeding issues related to maternal use of oral IS should be addressed before delivery. Ideally, myasthenic women considering pregnancy should seek prepregnancy counseling early on from their neurologist to maximize clinical improvement, minimize the use of IS, and address the need for thymectomy. Patient compliance, the presence of comorbidities (such as thyroid disease, diabetes mellitus, and hypertension), and the availability of resources all are important factors in the successful management of MG in women. Patients should be made aware of the issues and risks related to pregnancy and should make an informed decision based on the most current information available. They also should know that the effect of pregnancy frequently is variable and unpredictable and that the clinical state at onset of pregnancy does not predict the course of MG reliably.

Treatment of myasthenia gravis during pregnancy

The therapeutic regimen for myasthenic women who are pregnant or planning a pregnancy should be individualized based on the severity and distribution of muscle weakness. Weakness involving bulbar and respiratory muscles generally should be treated more aggressively because of the potential for life-threatening exacerbations endangering mother and fetus.

Thymectomy during pregnancy has no role because of its delayed effect and possible surgical risk. If thymectomy is indicated, it should be planned before pregnancy or after the postpartum period.

Cholinesterase inhibitors alone can be used in the mildest cases. Pyridostigmine is considered safe during pregnancy when used at the recommended dosage of less than 600 mg/d. There is no evidence of increased incidence of malformations in the offspring of rats treated with pyridostigmine during pregnancy and its use is not associated clearly with teratogenic effects in humans [2]. An isolated case report documents severe neonatal MG (NMG), growth retardation, microcephaly, joint contractures, and dysmorphic features in an infant born to a myasthenic mother who was taking four to eight times the recommended daily dosage of Pyridostigmine during pregnancy (1,500 to 3,000 g/day) [3].

Dosage adjustments may be required more frequently than usual because of blood volume and renal clearance changes. Intravenous administration should be avoided because of the potential increase in uterine contraction and premature labor. Plasmapheresis or IVIG can be used to manage severe MG symptoms or crisis during pregnancy or to avoid the use of IS with potential teratogenic effects [4]. The frequency of the treatments should be guided by the clinical course. The potential risks related to these treatments should be weighed against the severity of myasthenic weakness [5].

With plasmapheresis, there is a theoretic risk of inducing premature labor because of the removal of circulating hormones. Fetal monitoring during the third trimester is recommended. Monitoring of fluid balance and using a left lateral decubitus position during the procedure are helpful in avoiding hypotension.

The safety of IVIG use during pregnancy has not been investigated in MG, but the obstetric literature contains many reports of IVIG therapy for various conditions encountered during pregnancy, including autoimmune thrombocytopenia purpura, antiphospholipid syndrome, and neonatal alloimmune thrombocytopenia. IVIG infusions seem to be well tolerated and the occurrence of major and minor side effects is uncommon [6]. Specific contraindications to IVIG use include a previous episode of IVIG-induced anaphylaxis and selective IgA deficiency. Serious side effects include aseptic meningitis, acute renal failure, thromboembolic events, and anaphylactic reactions. Hyperviscosity and volume overloading associated with IVIG infusion may be of greater significance in pregnancy. Less severe but more common side effects include headache, nausea, and fever.

Corticosteroid therapy is effective in the majority of myasthenic patients and should be considered an option in pregnant women in whom the severity of symptoms makes the use of immunosuppression necessary. Prednisone presents little if any teratogenic risk to the fetus [7–10] and only a slight increase (less than 1% incidence) of cleft palate is associated with its use [11]. Premature rupture of the membranes may be associated with high-dose corticosteroid treatment [12,13].

Initiation of IS other than corticosteroids should be avoided before and during pregnancy whenever possible because of potential teratogenic effects. The long latency of AZA also makes initiation of this drug during pregnancy not useful. The risk of triggering MG exacerbation or crisis by discontinuing or decreasing IS in women already taking them when they become pregnant needs to be balanced against the risk of possible adverse side effects on the fetus.

Women who have MG and are taking AZA generally are advised against pregnancy, although there has not been a definite demonstration of teratogenicity in humans at therapeutic dosages and many normal pregnancies are reported while on the drug. Batocchi et al report four patients who had MG and were taking AZA during pregnancy, all of whom gave birth to normal babies. In one patient, the sudden withdrawal of AZA

had no effect on the MG course, whereas it induced severe exacerbation of MG symptoms in another [12]. AZA is reported to be safe during pregnancy in inflammatory bowel disease [14]. During 40 years' experience with AZA as an IS in organ transplant patients, the National Transplantation Pregnancy Registry identified no predominant or specific fetal malformation pattern attributable to this drug, and the epidemiologic data available to date are favorable in the setting of a category D agent [15]. Retrospective review of pregnancy outcomes reveals that infants exposed to AZA in utero might develop reversible leukopenia, anemia, thrombocytopenia, reduced immunoglobulin levels, infection, or thymic atrophy [16]. Other reports also indicate that babies born to mothers receiving AZA have increased risk of myelosuppression and immunosuppression [17–19].

Cyclosporine does not seem to be a major human teratogen and a recurrent pattern of congenital anomalies has not been observed. The general consensus is that the magnitude of the teratogenic risk for malformations is minimal, but there is a small to moderate risk of spontaneous abortions, prematurity, and low birth weight [15]. Although there is a growing number of case reports of transplant patients receiving cyclosporine who became pregnant and deliver a normal child, additional clinical data are needed before possible reproductive risk of cyclosporine can be determined definitely. The use of cyclosporine during pregnancy generally is discouraged in myasthenic women.

MMF in dosages equivalent to those used clinically in transplant patients causes fetal resorptions and malformations in pregnant rats and rabbits, predominantly defects of the head and eyes. These malformations are found in the absence of maternal toxicity [20]. Experience in transplant patients still is limited, as MMF is a newer agent [21]. Only six reports of live births to patients taking MMF are reported by the National Transplantation Pregnancy Registry; none of these reports found major malformations in the offspring, but all were born prematurely. The only possible teratogenic effects detected were hypoplastic nails and short fifth fingers in one newborn of a mother who received a kidney transplant during the first trimester of pregnancy and took MMF, tacrolimus, and prednisone for prevention of organ rejection. MMF should not be used in pregnancy until more information becomes available.

Methotrexate is a folic acid antagonist and should not be used to treat MG in women of childbearing age because of its association with congenital malformations, especially those involving the central nervous system [22].

Effect of pregnancy on the course of myasthenia gravis

Pregnancy may change the course of MG, frequently in an unpredictable way. The clinical state at the beginning of pregnancy does not predict occurrence of exacerbation or remission. Each pregnancy has its effect on MG symptoms and does not predict the course of subsequent pregnancies

[23]. New onset MG may occur during pregnancy or the immediate postpartum period. Worsening of MG symptoms occurs in approximately one third of pregnant patients and, although possible at any time during pregnancy, it is more likely in the first trimester [23,24]. Sudden and frequently severe exacerbations, including respiratory insufficiency, may occur in the first 3 weeks post partum and, therefore, frequent monitoring of MG signs and symptoms and timely adjustment of treatment are recommended during that time. The sudden drop in alpha-fetoprotein (AFP) concentration is implicated as a possible cause of this phenomenon. The mortality risk of pregnant MG women tends to correlate inversely with the duration of the disease, the highest risk in the first year and the lowest risk approximately 7 years from the onset of disease [25]. Myasthenic women who experience exacerbations during the puerperium have significantly shorter disease duration those who do not [26].

Improvement usually is observed in approximately 20% to 30% of pregnant women during the second and third trimesters, likely secondary to the immunosuppression that takes place in those phases of gestation. Complete remission may occur in some patients during late pregnancy. SFEMG demonstrates electrophysiologic changes concordant with the clinical fluctuations associated with pregnancy [27].

Batocchi et al, in their series from Italy, reported the course and outcome of 64 pregnancies in 47 women who had known MG. In patients receiving therapy before conception, MG symptoms improved in 39% of pregnancies and remained unchanged in 42%. Worsening was observed in 19% of cases and occurred predominantly during the first trimester (60%). After delivery, MG symptoms deteriorated in 28% of women. There was no correlation between MG severity before conception and exacerbations during pregnancy. The clinical course of MG during one pregnancy did not predict the course during subsequent pregnancies, supporting the impression that the disease remains highly variable and unpredictable during gestation [12]. Puerperium complications, especially infection, seem to increase the risk for exacerbations of MG symptoms, and respiratory and urinary tract infections therefore should be recognized and treated promptly [26].

The largest available review of the literature, by Plauche [24], shows a higher occurrence of exacerbation during gestation (41%) and in the puerperium (30%). This may be due to the inclusion of several case reports biased toward myasthenic pregnancies that had complications or crises [2] or could reflect a difference due to current more aggressive care. Maternal death was 4% in this review [24].

Labor and delivery

MG usually does not change the course of the first phase of labor, as it does not affect smooth muscle. Striated muscle, involved in the voluntary expulsive effort of the second phase of labor, may be prone to fatigue and

the obstetrician should be prepared to assist in this stage, if needed, with forceps or vacuum extraction. Myasthenic fatigue occurring during labor can be helped by cholinesterase inhibitors. These should be administered parentally because of unpredictable gastric absorption. Neostigmine doses of 1.5 mg intramuscularly or 0.5 mg intravenously are equivalent to 60 mg of pyridostigmine taken orally.

Although spontaneous abortion in the first trimester may improve myasthenic exacerbation, elective cesarean section can cause acute worsening of MG symptoms and should be performed only when necessary because of obstetric indications.

Magnesium sulfate for the management of eclampsia should be used cautiously in myasthenic women, as it can precipitate weakness by interfering with neuromuscular transmission. Maternal deaths are reported in myasthenic women who have received magnesium sulfate for pre-eclampsia.

Because myasthenic patients are sensitive to many anesthetic agents, epidural anesthesia is preferred in vaginal and surgical delivery. Non-depolarizing muscle relaxants may cause a prolonged or exaggerated reaction in patients who have MG and should be avoided whenever possible.

The effect of pre-existing MG on delivery and newborn outcome was examined in a recent study by Hoff et al, using data from the Medical Birth Registry of Norway from 1967 to 2000, including 127 births in 79 myasthenic mothers [28]. In this large population-based cohort study, women who had MG had an overall increased rate of delivery complications and a higher rate of intervention during delivery. Premature rupture of the membranes was the only single complication to occur more frequently. Mean gestational weight, neonatal mortality, and prematurity did not differ significantly between the MG and the reference group. Severe birth defects were observed in 3.9% of the 127 newborns of MG mothers compared with 1.9% of the ones in the reference group. Perinatal mortality was not increased significantly in the MG group versus the reference group (2.4% versus 1.4%).

The effect of maternal myasthenis gravis on the fetus and neonate

Transient neonatal myasthenia gravis

Transient NMG is a syndrome that affects 10% to 20% of newborns of myasthenic mothers and occurs shortly after birth [24,29–32]. Symptoms develop most commonly 12 to 48 hours after birth and include generalized weakness and hypotonia, difficulty feeding, feeble cry, ptosis, facial paresis, and respiratory distress. The delayed onset of NMG symptoms possibly is the result of transfer of water-soluble anticholinesterase medications from the mother to the newborn and AFP. AFP has a powerful inhibitory effect

on the AChR Ab binding capacity and high AFP levels therefore may protect the majority of newborns from developing clinical NMG [33]. The clinical improvement or remission commonly observed in myasthenic mothers during the second and third trimesters also may be the result of the high concentration of AFP in maternal serum from increasing placental permeability to fetal placental proteins that occurs with advancing gestation [34]. A similar effect attributed to AFP also is observed in other autoimmune diseases.

The severity of NMG symptoms varies among babies, with some showing only mild hypotonia and others having respiratory weakness severe enough to require assisted ventilation. The syndrome usually resolves within 1 month (18 to 21 days) but occasionally persists for as long as 4 months. All newborns of myasthenic mothers should be observed carefully during the first few days post partum for signs of muscle weakness and impaired bulbar and respiratory function. Ventilatory support and care in a neonatal ICU should be available at the time of delivery to avoid delaying supportive care. NMG symptoms respond to anticholinesterase medications and improve progressively as the antibody titer gradually falls. Anticholinesterase medications and ventilatory support should be used as necessary until the weakness resolves. Plasmapheresis should be considered in very severe cases.

NMG is caused by transplacental passive transfer of circulating nicotinic AChR Abs from the myasthenic mother to the fetus. In general, a correlation between the occurrence and severity of NMG and overall high AChR Ab titers in the mothers and in the newborns is observed. Exceptions are not infrequent, however, and cases of myasthenic mothers who do not have detectable AChR Abs and have had babies who have NMG are reported [35,36]. The severity of maternal MG symptoms does not correlate with the severity of NMG in the newborn, and NMG can occur in infants of myasthenic mothers who are in clinical remission. A high ratio of antiembryonic AChR to antiadult muscle AChR Abs correlates with the occurrence of NMG and suggests a predominant role of the antiembryonic form of AChR Ab in the pathogenesis of NMG [37,38].

When counseling pregnant myasthenic women, it is important to explain that it is not possible to predict precisely the occurrence and severity of NMG and it is unclear why some infants are affected clinically whereas others remain asymptomatic, even though they have detectable AChR Abs.

Arthrogryposis

Placental transfer of antibodies against the fetal AChR can cause arthrogryposis multiplex congenita (AMC) in some infants born to myasthenic women. The syndrome consists of nonprogressive multiple congenital joint contractures developing in utero from lack of fetal movements, preventing normal joint formation. Some infants born with AMC have survived, but AMC can lead to intrauterine fetal death or

neonatal death because of pulmonary hypoplasia and polyhydramnios [39–41]. AMC may occur even in asymptomatic mothers and recurrent cases are reported in sibships [42]. Ultrasound testing should be used to monitor fetal movements and to detect the development of joint contractures in utero.

AMC and its high risk of recurrence should be discussed among the possible complications of MG when counseling pregnant women. It also should be emphasized that the absence of myasthenic symptoms in the mother does not guarantee the birth of a normal newborn.

The potential role of plasmapheresis and immunosuppression during early pregnancy in preventing the occurrence of AMC and improving the outcome of newborns is not known [43].

A more complex phenotype with dysmorphic facies, abnormal genitalia, central nervous system atrophy, and lung hypoplasia also is reported in offspring born with AMC from myasthenic mothers.

Immunosuppressive therapy and lactation in myasthenia gravis

The American Academy of Pediatrics classifies pyridostigmine, prednisone, and prednisolone as compatible with breastfeeding [44]. Large doses of anticholinesterase drugs may cause gastrointestinal symptoms in the breastfed newborn. Some clinicians recommend that mothers wait at least 4 hours after taking their corticosteroid dose before nursing.

The question as to whether or not it is safe for women receiving IS other than corticosteroids to breastfeed is not answered completely. More information is needed, especially for newer agents, such as MMF, for which no data currently are available in regard to lactation effects.

IS are excreted in breast milk but it is not clear if such breast milk concentrations are significant biologically or have any substantial clinical effects on the infant. Breastfeeding generally is not recommended for mothers taking AZA, cyclosporine, or methotrexate.

AZA is excreted into breast milk in small amounts. No abnormalities in blood analysis or growth rate were found in three infants breastfed by mothers receiving immunosuppressant doses of AZA after renal transplantation [45,46]. Undetectable levels of 6-mercaptopurine (the active metabolite) in the milk were found in nursing women on AZA [22]. Despite these reports, breastfeeding while receiving AZA is not recommended by the World Health Organization (WHO) Working Group on Drugs and Human Lactation [47].

Estimates of neonatal exposure to cyclosporine in breast milk indicate it is likely to be far less than the levels to which the fetus is exposed prenatally [48]. In a group of seven infants breastfed by mothers receiving cyclosporine, it was estimated that the infants ingested less than 300 μg per day of cyclosporine, and all infant blood levels were below 30 ng/mL, the detection limit of the drug assay [49]. There were no demonstrable nephrotoxic effects or other side effects in these or other infants exposed to cyclosporine in

breast milk [48,49]. In a single case report, cyclosporine levels were undetectable in a neonate at various times during 10.5 months of exclusive breastfeeding from a woman on cyclosporine therapy [50].

Methotrexate is excreted in breast milk in small quantities [51]. Although the amount of methotrexate ingested daily through milk is less than 0.5% of the pediatric therapeutic dosage of this drug (0.12 mg/kg), the American Academy of Pediatrics lists methotrexate as contraindicated during breastfeeding [44], and the WHO Working Group on Drugs and Human Lactation does not recommend breastfeeding during the maternal use of this drug, unless no alternative is available [47].

Because human breast milk confers many benefits for the infant, advice to mothers should review the risk of the drugs against the disadvantages of formula feeding. Some mothers also find that loss of sleep from night feeding worsens symptoms of MG and choose not to breastfeed so they can have help with infant care.

Summary

Treatment considerations for women who have MG and are of childbearing age are complicated. When possible, before pregnancy, establishing a plan for therapy is ideal, recognizing the potential concerns for the patient and the fetus. Decisions about treatment during pregnancy must balance the potential complications for the fetus, the patient, and even the integrity of the pregnancy. Most women who have MG are able to complete pregnancy successfully and deliver a healthy baby; however, there always is some risk that NMG may occur. Pregnant patients who have MG are served best at centers capable of providing coordinated expert care from neurologic, obstetric, and pediatric providers.

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