

# Myasthenia gravis during pregnancy

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### Abstract

**Question** One of my patients who has been diagnosed with myasthenia gravis (MG) is planning pregnancy. Her MG is controlled with medications. Can her condition or her medications adversely affect her pregnancy?

**Answer** The course of MG during pregnancy is unpredictable, but there is no evidence that MG can adversely affect pregnancy outcomes. Examination of most of the medications used for symptom control has so far shown reassuring results. Prepregnancy thymectomy might decrease the need for medications during pregnancy. The newborn should be carefully monitored for signs of transitory MG.

### Myasthénie grave durant la grossesse

#### Résumé

**Question** Une de mes patientes a reçu un diagnostic de myasthénie grave (MG) et elle planifie une grossesse. Sa MG est contrôlée par pharmacothérapie. Son état ou ses médicaments peuvent-ils avoir des effets défavorables sur sa grossesse?

**Réponse** L'évolution de la MG durant la grossesse est imprévisible, mais il n'existe pas de données probantes à l'effet que la MG puisse influencer négativement l'issue de la grossesse. Les résultats des études sur la plupart des médicaments utilisés pour le contrôle des symptômes sont jusqu'à présent rassurants. Une thymectomie avant la grossesse pourrait réduire la nécessité de prendre des médicaments durant la grossesse. Il faudra surveiller attentivement le nouveau-né pour détecter tout signe de MG transitoire.

Myasthenia gravis (MG) is an autoimmune disorder affecting nearly 1 million individuals worldwide.<sup>1</sup> It is twice as common among women as it is among men,<sup>2</sup> diagnosed typically in the second and third decades of life. Myasthenia gravis is characterized by muscle weakness caused by impaired function of the acetylcholine (ACh) receptors at the neuromuscular junction<sup>1,3</sup> as a result of autoantibodies acting against the ACh receptors.<sup>3,4</sup> Hyperplasia and tumours of the thymus can cause the abnormal production of these autoantibodies.<sup>4</sup> Diagnosis of MG is made following clinical and physical examination and is confirmed by serum immunoassays to measure autoantibody levels.<sup>3,4</sup>

### Effect of pregnancy on MG

Owing to its high prevalence in women of childbearing age, and because it does not affect fertility in women,<sup>5</sup> it is not uncommon to see pregnant women with MG. The effect of pregnancy on MG varies considerably among women and even between pregnancies in the same woman.<sup>2</sup> During pregnancy, symptoms worsened for 41% of women with MG, while 30% showed no change, and 29% had remission of symptoms.<sup>6</sup> Improvement of symptoms during the second and third trimesters has been attributed to normal immunosuppressive changes

in late pregnancy.<sup>3</sup> Exacerbations of symptoms are most likely to occur in the first trimester or following delivery.<sup>6</sup> The risk of maternal mortality is highest during the first year after diagnosis of MG, with the risk being minimal 7 years after diagnosis.<sup>5</sup> Thus, women with MG should delay pregnancy for at least 2 years after disease onset.<sup>5,6</sup> Despite these considerations, pregnancy has not been shown to adversely affect MG in the long term.<sup>7</sup>

### Effect of MG on pregnancy

In general, MG does not have any severe adverse effects on pregnancy.<sup>2</sup> Reports do not suggest an increased risk of spontaneous abortions or premature births for women with MG.<sup>6,8</sup> In contrast, it is possible for infants to develop transient neonatal MG. This happens in 10% to 20% of cases owing to placental transfer of immunoglobulin G antibodies in the second and third trimesters.<sup>7</sup> The neonate typically develops symptoms 2 to 4 days after birth, including respiratory problems, muscle weakness, feeble cry, poor sucking, and ptosis, necessitating close monitoring.<sup>3,5,7</sup> This condition usually reverses itself after 3 weeks<sup>5</sup> without complication, owing to degradation of the antibodies derived from the mother.<sup>3</sup>

### Mode of delivery

As the uterus is made up of smooth muscle, it is not affected by presence of ACh receptor antibodies, and vaginal delivery is recommended for women with MG.<sup>3,7</sup> Assistance might be required in the second stage with the help of forceps or vacuum extraction, as striated muscles are involved during this stage and these muscles can be affected by the ACh receptor antibodies.<sup>2,7</sup> Cesarean section should be performed only for obstetric indications, as surgery can be stressful for women with MG.<sup>3,7</sup> Epidural anesthesia is recommended during labour and delivery<sup>5,7</sup> because neuromuscular drugs and narcotics can potentiate ACh receptor antibodies' effects on the neuromuscular junction.

### Management

Optimal management of MG for pregnant women should involve obstetricians and neurologists. Nearly 15% of individuals with MG have thymomas,<sup>1</sup> and about 60% to 80% present with hyperplastic thymus.<sup>2</sup> Thymectomy has become a standard treatment protocol for patients with MG and thymomas or hyperplasia of the thymus.<sup>1,2</sup> Five years after thymectomy, complete remission of MG has been seen in nearly 45% of patients.<sup>9</sup> During pregnancy,

women who have not undergone thymectomy present with higher incidences of exacerbations when compared with those who have undergone thymectomy.<sup>7</sup> Furthermore, infants born to those who had undergone thymectomy had less risk of developing neonatal MG.<sup>8</sup> Thus, women with MG planning pregnancy should be advised to undergo thymectomy before becoming pregnant.<sup>8</sup>

Pharmacologic treatment for MG is usually centred on increasing the levels of ACh and decreasing the production of auto-antibodies. Pharmacologic treatment should not be stopped during pregnancy; however, it might need to be altered depending on disease severity or exacerbations.<sup>2</sup>

Acetylcholine esterase inhibitors, such as pyridostigmine and neostigmine, are frequently used in treatment of MG.<sup>1-3</sup> Although data regarding acetylcholine esterase inhibitor use during pregnancy are limited, the available evidence does not suggest an increased risk of malformation or other adverse pregnancy outcomes. There was one case report of microcephaly attributed to pyridostigmine use.<sup>10</sup> However, the mother had been taking doses 4 to 8 times the recommended dose.<sup>10</sup> Further, in a response to this report, some authors

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suggested that placental transfer of maternal antibodies, not the pyridostigmine, might have caused the fetal anomalies.<sup>11</sup> Their claim is supported by studies that show safe use of pyridostigmine by women with MG during pregnancy.<sup>5,8,10</sup>

Corticosteroids such as prednisone and its biologically active compound prednisolone are commonly used in MG.<sup>11</sup> A Motherisk meta-analysis determined an increased odds ratio (OR) of oral cleft with corticosteroids (OR=3.69, 95% CI 2.15 to 6.32). Although the summary OR of cohort studies was not significant (OR=2.74, 95% CI 0.96 to 7.82), the cohort studies showed a clustering of cleft palate when compared with the controls.<sup>12,13</sup> Women with MG who are prescribed corticosteroids must be informed before conception of the increased risks of oral clefts. It is important to note that the formation of the palate is complete in the fetus by week 12.<sup>14</sup> Thus, one option is to commence corticosteroid therapy after week 12.

Azathioprine (AZA) has not been associated with increased rates of congenital abnormalities.<sup>15</sup> However, there is evidence of possible intrauterine growth retardation and infants with low birth weight, and concern about immunologic changes.<sup>15,16</sup> Despite these reports, it is difficult to determine whether AZA is the sole cause of these adverse outcomes or whether they are due to the underlying maternal condition or to other drugs used in combination with AZA to treat the mother.<sup>17</sup> In addition, initial findings from an ongoing study by Motherisk assessing neurodevelopment in children exposed to AZA in utero do not suggest significant effects on IQ compared with unexposed children.<sup>18</sup>

Although cyclosporine has been shown to cross the placenta readily, there has been no evidence that it is associated with increased risk of severe complications or malformations.<sup>3,11</sup> A recent Motherisk study found that renal transplant patients who were taking cyclosporine therapy had a higher rate of preterm delivery, which was associated with lower birth weight in the neonates of these women.<sup>19</sup> However, assessment of long-term neurodevelopment outcomes in cyclosporine-exposed children did not reveal any significant differences compared with unexposed children.<sup>19</sup> Hence, cyclosporine therapy can be used during pregnancy in which the benefit to the mother outweighs the risk to the fetus.<sup>20,21</sup>

Rituximab readily crosses the placenta at about 16 weeks' gestation.<sup>21</sup> To date, there have not been any reports of major malformations attributed to rituximab exposure.<sup>22</sup> There were some cases of decreased B-cell counts in infants born to women using rituximab, but this condition resolved within 6 months.<sup>22</sup>

Mycophenolate mofetil (MMF) is a second-line drug for treatment of mild forms of MG.<sup>1</sup> Recently MMF was reclassified by the Food and Drug Administration as a class D drug, indicating that there is evidence of

teratogenicity in human fetuses.<sup>23</sup> It is associated with first-trimester miscarriage and structural malformations of the ears and jaw, cleft lip and palate, as well as hypoplastic fingers and toenails.<sup>24-26</sup>

In addition to these drugs, medications that exacerbate symptoms of MG by potentiating the effect of ACh receptor antibodies are contraindicated in patients with MG. These drugs include neuromuscular blocking agents (eg, magnesium sulfate), antiarrhythmic drugs (eg, quinidine), and local anesthetics (eg, esters), as well as antibiotics from the aminoglycoside, quinolone, and macrolide classes.<sup>27</sup>

## Conclusion

There is no evidence that MG can adversely affect pregnancy outcomes, and most of the medications used for symptom control appear to be relatively safe during pregnancy (except for MMF, used as second-line therapy). Prepregnancy thymectomy might decrease the need for medications during pregnancy. The newborn should be carefully monitored for signs of transitory MG. 🌿

### Competing interests

None declared

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