

## **Pregnancies Complicated by Myasthenia Gravis**

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**Objective:** To estimate the incidence of myasthenia gravis in Bahrain, to assess its effect on the course of pregnancy and a report of four pregnancies in two women who were treated for myasthenia gravis during pregnancy.

**Design:** Retrospective review of all myasthenia gravis.

**Methods:** Retrospective review of all cases of myasthenia gravis admitted at Salmaniya Medical Complex between 1<sup>st</sup> January 1990 and 14<sup>th</sup> April, 2001 and present four pregnancies and two abortions in two patients treated for myasthenia gravis.

**Results:** Fifty five cases of myasthenia gravis were admitted to Salmaniya Medical Complex between 1<sup>st</sup> January 1990 and 14<sup>th</sup> April, 2001. Thirty two were females in their reproductive period of their life. Only two women were treated during six pregnancies (four live births, two terminations of pregnancies), giving an incidence of 1:15,000 deliveries. None of the four babies born were affected by myasthenia gravis and the disease did not affect the course of the pregnancies.

**Conclusions:** No congenital abnormalities were discovered in the four babies delivered at our institution. Plasmapheresis, IV. immunoglobulin and immunosuppressive drugs can be administered safely if needed.

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Myasthenia gravis is an autoimmune disorder, which rarely occurs in women of childbearing age<sup>1-3</sup>. The disease affects the neuromuscular transmission causing muscle weakness and fatigability of the skeletal muscles<sup>4-6</sup>. Its cause is mostly due to elevated serum antibodies against acetylcholine receptors (anti-AChRab) at the motor end plate<sup>7,8</sup>. The incidence is reported to be more common in women in their second or third decades.

When it complicates pregnancy, the course of the illness is unpredictable<sup>11,12</sup>. Furthermore, the course of myasthenia gravis does not reflect the course in subsequent pregnancies<sup>13</sup>. Therapeutic abortion does not alter the symptoms<sup>14</sup>. There are some reports suggestive of an increase in the incidence of premature labour and pre-eclampsia in patients with myasthenia gravis<sup>15,16</sup>. A potentially problematic time is therefore during labour and delivery. Although the uterus itself is a smooth muscle<sup>17</sup>, independent of acetylcholine receptors, during the second stage of labour when voluntary efforts at foetal expulsion are required, the patient may tire quickly and may not be able to aid voluntary expulsive efforts. Forceps or vacuum extraction is often recommended in the final stages of labour<sup>18-20</sup>. Caesarean section usually is not required except when there is an obstetric indication. Low spinal or epidural anaesthesia are preferred if surgery is needed and the patient does not exhibit signs of bulbar or respiratory involvement<sup>21</sup>.

Our aim was to estimate the incidence of myasthenia gravis, assess its effect on the course of pregnancy and report four pregnancies in two women who were treated for myasthenia gravis.

## **METHODS**

The files of all cases of myasthenia gravis admitted in Salmaniya Medical complex between 1<sup>st</sup> January 1990 and 14<sup>th</sup> April, 2001 were reviewed and assessed. During the same period we have seen two patients with myasthenia gravis during their four pregnancies which were successfully managed and delivered four healthy babies while their mothers were on treatment.

## **RESULTS**

All cases of myasthenia gravis admitted into the Salmaniya Medical Complex between 1<sup>st</sup> January 1990 and 14<sup>th</sup> April 2001 were surveyed. It was found that 55 cases were registered. Of these, 32 (60%) were female and only two patients were treated during pregnancy, giving an incidence of 1:15,000 deliveries. This suggests that the condition is rare in pregnancy. None of the four babies born were affected by myasthenia gravis and the disease did not affect the course of the pregnancies.

## Case 1

### **Thirty one years old, Gravida 5, Para 3, Abortion 2 who was a known case of myasthenia gravis.**

Her problems began at the age of 18 years when she developed ptosis, diplopia, altered speech with a nasal twang, dysarthria and dysphagia. She also had fatigability while chewing food and manifested proximal muscle weakness of both upper and lower limbs. She was investigated and diagnosed as myasthenia gravis with positive acetylcholine receptor antibodies. She was treated with pyridostigmine (Mestinon) 60 mg orally every six hours. At the time of diagnosis she was discovered to be eight weeks pregnant. Her antenatal period was uneventful apart from the persistence of myasthenia gravis related symptoms. She delivered vaginally and was discharged home with the baby on the seventh postnatal day. One month after delivery her symptoms worsened and she was readmitted for treatment with steroids and parenteral neostigmine. Thymectomy was done under general anaesthesia and her postoperative period was uneventful. After surgery she was kept on Mestinon 90 mg orally five times daily and Prednisolone 60 mg daily for one month. The medicines were then tapered off and she was maintained on Mestinon 40 mg daily. She also needed plasmapheresis thrice that year. She improved gradually, but deviation of the eyes and diplopia persisted. She was then prescribed a higher dose of pyridostigmine 120 mg four times daily, Prednisolone 75 mg daily and Azathioprine 100 mg daily with good response.

The following year she again became pregnant, but decided to undergo termination because of the potential teratogenicity of the drugs she was taking. A year later she again became pregnant and another pregnancy was terminated at eight weeks because of her medications and the persistence of difficulty in swallowing and speaking despite the combination therapy. The patient remained on the same medications for the next five years. She became pregnant again and she was advised to stop the immunosuppressive therapy: Azathioprine (Imuran) 150 mg daily and continue with Mestinon 90 mg QID and Prednisolone 30 mg daily. During pregnancy her progress was normal apart from gestational diabetes, which was treated with insulin. During delivery the patient was given parenteral Mestinon. She delivered a live and healthy female baby vaginally. Two days following the delivery the patient developed a second degree uterine prolapse. She was managed with a ring pessary on her postnatal visit. Since then the pessary has been replaced every six months until she became pregnant.

In her final pregnancy she had a relatively benign course and continued to take her medications, Mestinon and Prednisolone until 38 weeks she was admitted in early labour. The ring pessary was removed and this was followed by a rapid labour leading to spontaneous delivery of a live and healthy female baby. The postnatal period was uneventful and she was discharged with her baby on the fourth postnatal day.

## Case 2

### **Forty-three years old Gravida 3, Para 2, Abortion 0 Bahraini patient.**

The symptoms of myasthenia gravis started at the age of 32 years, one month following her second delivery. She felt then abnormally weak and developed some difficulty in swallowing, drinking or chewing. Speech became slurred, particularly later in the day. She also developed left-sided ptosis at times and double vision.

Electromyography (EMG) confirmed the diagnosis of myasthenia gravis. Serum contained acetylcholine receptor antibodies. The CT (computer tomography) scan revealed the presence of a thymoma. She was treated with Prednisolone 5 mg in increasing doses up to 60 mg daily and Neostigmine (Prostigmine) given subcutaneously 250 mg was repeated every 4-6 hours. Pyridostigmine (Mestinon) was also prescribed. Minor bulbar symptoms in the form of some dysarthria and minimal dysphasia still remained. Therefore two plasmaphereses were undertaken prior to her surgery. Thymectomy was performed and a typical thymoma was removed. After surgery she continued to take Prednisolone 60 mg daily for 10 days with pyridostigmine (Mestinon) 60 mg 4 hourly from noon. Her condition remained stable and eventually the dosage of her medicines was tapered. During the interim period until her latest pregnancy she did not need any immunosuppressive drugs.

Her current pregnancy was uneventful apart from two antenatal admissions at 33 and 37 weeks of gestation because of pregnancy induced hypertension. She had requested to have sterilization should Caesarean section be needed. The patient was not seen further until two weeks postnatally. She went to the United Kingdom for delivery where she had a spontaneous vaginal delivery in a private hospital. The puerperium was uneventful.

## **DISCUSSION**

Myasthenia gravis has a prevalence rate of approximately 1 in 10,000 to 50,000. The disease affects both sexes, but in those who develop the disease before 40 years of age, females are affected two to three times more frequently than males. The peak onset of myasthenia gravis in women is at 20 to 30 years of age. Women with myasthenia gravis have a higher incidence of other autoimmune disorders such as rheumatoid arthritis, autoimmune thyroiditis and systemic lupus erythematosus (SLE). The course of the disease is unpredictable and varies in intensity between pregnancies.

Myasthenia gravis is rare at our institution. We have found only 55 cases registered in nearly 10 years period. Thirty two (60%) were females and only 2 cases were treated during pregnancy which means an incidence of 1:15,000 deliveries.

A typical clinical presentation includes diplopia and ptosis as initial complaints. Other facial muscle weakness could occur, producing difficulty in chewing, speech and swallowing. Approximately 85% of patients eventually exhibit generalized limb muscle

weakness, which is usually proximal and often asymmetric. On occasion, weak respiration or swallowing could become severe enough to require respiratory assistance.

The diagnosis is supported by a positive edrophonium (Tensilon) test. A negative acetylcholine receptor antibody finding is not unusual, because only about 50% of patients with weakness confined to the ocular muscles have detectable acetylcholine receptor antibodies. Ten to 20% of patients with overall clinical evidence of myasthenia gravis have no detectable antibody in their serum. Treatment modalities are usually limited to the use of cholinesterase inhibitors, thymectomy, steroid/cytotoxic immune suppressive agents and plasmapheresis. Most patients are maintained on acetylcholinesterase inhibitors, the most common of which is neostigmine. At physiologic pH, neostigmine is ionised and therefore does not cross the placenta well. Furthermore, it is not a known teratogen. Doses of neostigmine must be adjusted during pregnancy because of increased volume of distribution and increased clearance.

Nearly one third of the patients with myasthenia gravis improve during pregnancy, one third remain the same and the remainder have worsening of their symptoms. Therapeutic abortion does not alter the symptoms. In patients who have had multiple pregnancies, the course of myasthenia in previous pregnancies does not reflect its course in a subsequent pregnancy. There are some reports that suggest a slightly higher risk of prematurity and/or premature labour in patients with myasthenia. A potentially problematic time for myasthenic patients is often during labour and delivery. Although the incidence of pre-eclampsia is not increased in the myasthenic patient, if the patient has concomitant pre-eclampsia, use of magnesium sulphate should be avoided since this drug decreases the amount of transmitter liberated at the motor nerve terminal. This diminishes the depolarising action of acetylcholine at the endplate and depresses excitability of the muscle fibre.

With respect to foetal considerations, no congenital malformations or other neonatal injury have been attributed to maternal treatment with cholinesterase inhibitors. This is also true of corticosteroid therapy. In addition, prednisone crosses the placenta very poorly. Thymectomized patients had a more stable course than non-thymectomized patients. There was no difference in the development of neonatal myasthenia gravis between these populations. Plasmapheresis has been used during pregnancy without any apparent adverse effects to the foetus. Occurrence of neonatal myasthenia cannot be predicted by the course of severity of the disease in the mother, by the presence or absence of thymectomy, or by the level of maternal anticholinesterase receptor antibodies. In fact, some mothers in complete remission may occasionally have neonates with transient myasthenia gravis. There is some evidence that mothers who have had one child with neonatal myasthenia gravis are at an increased risk for having a second child developing the same symptoms.

There are rare reports of congenital malformations in children of mothers with myasthenia gravis who have not received corticosteroids or other immunosuppressant drugs. These may include arthrogryposis, hypognathism, polydactyly and hypogammaglobinaemia. These congenital anomalies are so infrequent that they may

well not be attributed to myasthenia gravis alone. There appears to be no absolute contraindication to the use of any of the commonly used medications in myasthenic mothers who are breast-feeding.

**Anaesthetic considerations:** Most authorities recommend the use of intramuscular injections of neostigmine during labour, but others maintain this is unnecessary and advocate intravenous injection to provide less fluctuation in clinical symptoms<sup>22</sup>. However, intravenous administration of anticholinesterase drugs has been reported to cause premature labour, so they should be administered carefully<sup>23</sup>. It should also be noted that anticholinesterases potentiate vagal responses and that vagolytic agents should be immediately available<sup>20</sup>. When given parenterally, as during labour, the ratio of oral to parenteral dosage is 30:1<sup>24</sup>.

When the edrophonium test indicates myasthenic crisis, the cautious intravenous administration of neostigmine or pyridostigmine can be tried, keeping in mind their potential to increase uterine tone and contractility. Neostigmine, 0.3 mg, or 1.2 mg pyridostigmine should be initially administered and subsequent doses of half such amounts should be given 3 to 5 minutes apart if needed<sup>25</sup>. Since edrophonium may produce increased oropharyngeal secretions and further weakness of striated muscles, the testing location should be equipped for airway resuscitation. The anaesthetist should also be aware that atropine, used to reduce the muscarinic side effects of the anticholinesterases, could mask side effects that signal excessive dosage<sup>26</sup>.

Electrocardiography testing is recommended because myocardial lesions have been described in these patients<sup>21,25</sup>. Sensory changes both in involved or uninvolved muscle groups are frequently present in myasthenia gravis. Common complaints include lower back pain, headache, ocular pain and paraesthesias of the face, lips, tongue and extremities<sup>25</sup>. These obviously should be noted before the administration of any anaesthetic agent. Since the incidence of hyperthyroidism is frequently associated with myasthenia gravis, any symptoms of thyroid dysfunction warrant thyroid function testing.

In terms of management for delivery, the anaesthetist and obstetrician should first be aware that respiratory compromise in the myasthenic patient may render her more susceptible to the depressant effects of narcotic drugs, barbiturates, tranquillisers and volatile anaesthetic agents. It is not clear in the literature whether myasthenic patients have a true increased sensitivity to these drugs. Regardless, all depressant medications should be given judiciously.

Since uterine smooth muscle is not involved in the myasthenic process, vaginal delivery is the most common route of delivery. Because of its ability to eliminate the stress response to pain and the need for systemic (and potentially respiratory depressing) medication, regional analgesia is usually preferred<sup>21,22,25,27</sup>. Although low spinal anaesthesia had been recommended in the past to avoid high blood levels of local anaesthetic, no evidence of increased sensitivity of the neuromuscular junction to local anaesthetics in myasthenia gravis patients has been found<sup>25,27</sup>. Both Rolbin et al<sup>21</sup> and Coaldrake and Livingstone<sup>22</sup> have reported no difficulty in myasthenic patients receiving

epidural lignocaine in doses of 320 to 400 mg. Plasma cholinesterase enzyme activity could decrease in myasthenia gravis patients, therefore amide type local anaesthetics are theoretically thought to be a safer choice when used in large quantities, as with epidural anaesthesia<sup>20,21,25,28</sup>. Tetracaine has been reported to be safe for use in spinal anaesthesia, perhaps because of the relatively small dose required<sup>21</sup>.

The anaesthetist should also be aware that certain medications frequently administered during labour may be contraindicated in myasthenic patients (Table 1). The anaesthetist should also be aware that the patient could also be receiving chronic steroid treatment and therefore could require stress doses of steroids throughout labour.

Table 1: **Drugs contraindicated in the patient with myasthenia gravis**

<b>Antibiotics</b>
Gentamycin
Kanamycin
Streptomycin
Neomycin
Polymyxin
Colistin
Tetracycline
Lincomycin
<b>Cardiac drugs</b>
Quinidine
Propranolol
<b>Beta mimetics</b>
Ritodrine
Terbutaline
<b>Tocolytics</b>
Magnesium sulphate
<b>Others</b>
Quinine
Penicillamine
Lithium salts

Plasmapheresis may lead to a pronounced reduction in circulating antiacetylcholine receptor antibodies with dramatic improvement in symptoms. However it should be

noted that improvement lasts for only several days to three months<sup>20</sup>.

If it is electively determined that the patient requires Caesarean delivery, regional anaesthesia is recommended provided the patient does not have signs of bulbar or respiratory muscle involvement that would warrant protection of the airway via endotracheal anaesthesia. Good results have been reported using epidural anaesthesia with 2% lignocaine with and without adrenalin 1:200,000<sup>21,22</sup>. If general anaesthesia is required, an awake endotracheal intubation or induction and intubation under sodium thiopental (if the patient is very weak) may be performed. For intubation, 30 to 50 mg of succinylcholine may be used if needed<sup>21</sup>. Should intraoperative muscle relaxation be required, 1 to 3 mg doses of d-tubocurare are recommended.

Factors thought predictive of the need for postoperative mechanical ventilation are (1) duration of myasthenia; (2) history of chronic respiratory disease for >six years; (3) pyridostigmine dosage greater than 750 mg/day; and (4) vital capacity less than 2.9 L<sup>29</sup>. Either of the first two factors alone or any combination of two or more factors predicts this need. Since pharyngeal and neck muscles may have a delayed recovery despite the presence of a sustained tetanic stimulation, patients should be able to lift their head for 5 seconds and demonstrate an inspiratory force  $\geq 25$  cm H<sub>2</sub>O prior to extubation.

Postpartum exacerbations have been reported to be sudden and devastating, therefore the mother should be watched closely during her postpartum convalescence<sup>28</sup>. This is often a time for wide swings in anticholinesterases requirements and close measurements of vital capacity and other observations of muscle strength must be frequently assessed.

In the two cases reported here, there were four pregnancies and two abortions. The course of the disease was unpredictable and varied in intensity between pregnancies. Although one patient had terminated a pregnancy following a thymectomy, it is rarely indicated in cases of myasthenia.

A few reports have suggested the possibility of congenital abnormality in the neonate eg, congenital myasthenia, arthrogryposis or other autoimmune problems; none were found in the four children delivered to these two women.

## CONCLUSIONS

**The incidence of myasthenia gravis in Bahrain is 1:15,000 deliveries. No congenital abnormalities were discovered in the four babies delivered at our institution. This may be because of the small number of cases. Prenatal treatment with plasmapheresis, IV immunoglobulin and immunosuppressive drugs can be utilised safely in pregnancy. Steroids however are associated with premature labour. Nonobstetric surgery during pregnancy or surgery at the time of delivery requires special care in avoiding muscle relaxants and anaesthesia is preferably achieved with spinal or epidural blocks. Conduction anaesthesia is again the method of choice should Caesarean section or instrumental delivery be contemplated.**

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