Case study

Myasthenia Gravis in Pregnancy: Case series and review of literature

Abstract

Myasthenia gravis is a rare autoimmune disorder affecting the neuromuscular junction and is more common in the women during their second or third decade of life. The course of the disease in pregnancy is unpredictable and may aggravate warranting optimal preconceptional counselling, strict adherence to medication, recognition of complications, avoidance of precipitating factors, intensive antepartum and intrapartum care by multi-disciplinary team for successful outcomes and prevention of life-threatening complications. The pregnancy outcomes in patients with myasthenia gravis is discussed in this case series.

Keywords

Myasthenia gravis, pyridostigmine, neostigmine, anticholinesterase inhibitors, thymectomy

Introduction

Myasthenia gravis (MG) is a chronic autoimmune disorder that affects the post-synaptic portion of the neuromuscular junction by formation of antibodies against nicotinic acetylcholine receptors (AChR). The reported prevalence varies between 126 and 400 per million[1] and is more common in reproductive age group women, who constitute 65-70% of the affected[2].The condition may also be unmasked for the first-time during pregnancy necessitating clinical acumen about MG management protocols. The literature review shows mostly studies from the Western population with controversies on the disease course, role of thymectomy, safety profile of drugs, mode of delivery and data on neonatal myasthenia. This article aims to study the clinical presentation, management details and pregnancy outcomes in a tertiary care centre from Southern Indian population and provides a brief review of literature on myasthenia complicated pregnancies

Case details

Data of 14 pregnancies in seven women with MG who delivered in a tertiary care centre of Southern India was analysed. All pregnancies were managed by multidisciplinary team involving obstetrician, neurologist, anaesthetist and neonatologist at tertiary care level. The maternal and disease characteristics with management details are summarised in Table 1. Various pregnancy outcomes are enlisted in Table 2. One patient was diagnosed with MG for

the first time in pregnancy and others had onset of disease varying from 2 to 15 years prior to pregnancy. Four pregnancies had acute exacerbations and two had undergone prior thymectomy. There was one pregnancy loss at 20 weeks while rest of the pregnancies had successful outcomes. Seven women underwent caesarean section for obstetric indications. Two of the neonates showed signs of transient neonatal myasthenia gravis but there were no neonatal deaths or anomalies.

Discussion:

MG is characterised by fluctuant and progressive skeletal muscular weakness on repetitive movements. The commonest signs and symptoms include muscle fatigue, ptosis, dysphagia, speech difficulty and respiratory distress based on the muscle group involvement which intensifies as the day progresses and relieved by rest. Amongst seven women in the present study, all had ocular involvement, four women had limb weakness, two had respiratory involvement and one had oropharyngeal muscular group involvement characterising the various clinical presentation. There may be an overlap with other immunological conditions as in the present case series with one woman having associated hypothyroidism due to Hashimoto's thyroiditis.

MG in pregnancy can have altered course in pregnancy similar to other autoimmune disease conditions. Generally, one third of the pregnancies have exacerbations and in one third there may be no change. [3] Four in fifteen pregnancies had deterioration, with one in the second trimester, two in the last trimester and one in the puerperium. Two of the exacerbations followed urinary tract infection which may be an associated precipitating factor. The reactivation of the immunological response during labour and puerperium may also contribute to these events. In a study involving 69 patients by Djelmis et al., 30.4% patients had exacerbation during pregnancy with 14.5% in last four weeks of pregnancy and 15.9% in puerperium. [4] Mortality risk is considered to be inversely proportional to the duration of the disease with highest risk in the first year and minimal after seven years of onset. There were no maternal deaths in the present case series.

Higher incidence of abortions, premature rupture of membranes has been reported in literature. [5] There was one pregnancy loss at 20 weeks and rest of the pregnancies had successful outcome and there were no preterm deliveries or other obstetric complications in the present series. Anticholinesterases such as pyridostigmine 30 to 60 mg every fourth to eighth hourly and neostigmine are the mainstay of treatment and they are considered safe in pregnancy at recommended dose. Corticosteroids, azathioprine ad cyclosporine are used only when the symptoms are uncontrolled. Plasmapheresis and intravenous immunoglobulins are

used in MG crisis. Thymectomy is considered as a primary disease controlling modality resulting in complete remission in 40 to 50% of patients and is done prior to pregnancy. [6] In the index series, patient number four and six had undergone thymectomy two and ten years prior to the pregnancy but both had acute exacerbations in the last month of pregnancy. There are controversial reports with few studies stating fewer clinical exacerbations in pregnancy following thymectomy [7] while others have shown exacerbations. [3] Summary of the various pregnancy outcomes in MG on literature review is presented in Table 3.

Another area of concern is the exacerbation of the condition with certain drugs such as magnesium sulphate, morphine, clindamycin, ciprofloxacin, aminoglycosides, beta blockers, diazepam, phenytoin, tranquilizers and antipsychotic drugs. Prophylactic use of magnesium sulphate for preeclampsia is generally avoided as it may lead to respiratory depression but if mandated as in occurrence of eclampsia unresponsive to alternatives, then administration must be with extreme caution in consultation with anaesthetist/ neurologist and with ventilator standby.

Comprehensive antenatal care should be thereby provided encompassing frequent antenatal visits, neurologist consultation, antepartum fetal monitoring with daily fetal movement count, biophysical profile and non- stress test as recommended, monitoring of fetal growth parameters and treatment of infections. Arthrogryposis multiplex congenita is another known entity to occur with MG due to passage of AChR antibodies during pregnancy secondary to fetal akinesia which can be recognised with reduced fetal movements. [15]

Vigilant intrapartum monitoring should be done as stress of labour and exertion may cause deterioration. Epidural analgesia is recommended as opioids may cause exacerbated respiratory depression in MG. Adequate analgesia will alleviate the pain and reduce fatigue and weakness Parenteral neostigmine 1.5 to 2 mg intramuscularly is preferred in labour due to erratic gastric absorption. The choice of mode of delivery is as per the obstetric indication and second stage may be cut short by forceps wherein abdominal muscles are involved in bearing down. Caesarean section may be indicated in critically ill patients with respiratory involvement requiring mechanical ventilation. Five women underwent vaginal delivery with instrumental delivery in two and seven women underwent caesarean section for obstetric indication in the present case series.

The choice of anaesthesia would be regional anaesthesia unless with respiratory involvement. The neuromuscular blockade may be prolonged with the use of muscle relaxants such as succinyl choline. Local anaesthetics can be used but higher doses of ester

anaesthetics should be avoided. Inhalational anaesthetics such as halothane should be generally avoided. Similarly, Ketorolac is a better analgesic choice since opioids and sedatives are contraindicated. Severe exacerbations are also known to occur in the puerperium precipitated by puerperal infections. Epidural analgesia was used in two patients in the study cohort and all caesarean sections were done under regional (spinal in 5 and spinal with epidural in 2) anaesthesia. One of the patients had deterioration in puerperium managed with parenteral neostigmine 0.5 mg and intensive care.

Transitory neonatal myasthenia gravis (TNMG) occurs in 12 to 20% new-born of mothers with MG. [16] The clinical presentation usually develops in the first four days of life and includes lethargy, slow respiration, and generalised muscle weakness, absent Moro's reflex and weak cry. In the present series, two neonates showed features of TNMG and both the mothers had disease duration for approximately six years with conflicting evidence from literature that there is an inversely proportional relationship between incidence of TNMG and maternal disease duration. Breastfeeding is not contraindicated in women with MG and use of anticholinesterases, steroids are safe during lactation. Methotrexate, mycophenolate mofetil and cyclophosphamide are avoided during pregnancy and lactation.

Conclusion

The management of MG in pregnancy should ideally start preconceptionally aiming at optimising the disease status and avoiding teratogenic drugs. They can have exacerbations and crisis during pregnancy, thereby require close antenatal follow-up at a tertiary care centre. Prevention and prompt treatment of infections, avoidance of myasthenia precipitating drugs and intrapartum care by multidisciplinary team should be advocated. Caesarean section should be considered mainly for obstetric reasons only and choice of anaesthesia is regional as these patients are sensitive to many of the general anaesthetic inducing agents, muscle relaxants and opioids. New-born has to be monitored for signs of TNMG and exclusive breastfeeding must be encouraged.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Consent:

Written informed consent has been obtained from patients.

Competing interests

Authors declare that no competing interests exist.

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Table 1: Maternal and disease characteristics and management details

Patient details	Age at pregnancy	Age at diagnosis	Type of involvement	Comorbidities /Surgeries	Medication
Patient 1	21	19	Upper limb and lower limb weakness Respiratory Ocular	none	Tab.Pyridostigmine 60 mg TDS Tab.Neostigmine 15 mg sos. Tab.Prednisolone10 mg OD
Patient 2					
Pregnancy 1	25	22	Ocular		
Pregnancy 2	28			Hypothyroidism	Tab. Pyridostigmine 60 mg OD
Patient 3					
Pregnancy 1	30	30	Ocular	nil	Tab.Pyridostigmine 60 mg TDS
Pregnancy 2	33			nil	Tab.Pyridostigmine 60 mg TDS
Pregnancy 3	36			nil	Tab.Pyridostigmine 60 mg TDS

Patient 4					
Pregnancy 1	22	20	Ocular and limbs	Underwent thymectomy at 23 years of age	Tab. Pyridostigmine 60 mg TDS
Pregnancy 2	25				Tab.Neostigmine 30 mg Q4H
Patient 5	27	Diagnosed at 14 weeks	Ocular, difficulty in swallowing, all limbs weakness	nil	Tab. Neostigmine 15 mg QID Tab. Pyridostigmine 60 mg TDS
Patient 6					
Pregnancy 1	28	18	Ocular and limbs	nil	Tab. Prednisolone 5 mg BD Tab. Pyridostigmine 60 mg TDS
Pregnancy 2	30			GDM/ underwent thymectomy 10 years back	
Patient 7					
Pregnancy 1	26	16	Ocular	nil	T. Pyridostigmine 60 mg TDS
Pregnancy 2	28				
Pregnancy 3	31				

GDM- Gestational diabetes mellitus

Table 2: Pregnancy outcome in women with myasthenia gravis

Patient details	Complications in antenatal period	GA at delivery (weeks)	Mode of delivery/ indication	Birth weight (grams)	Neonatal complications	Puerperium
Patient 1	Nil	39	LSCS for pathological CTG	2800	nil	Exacerbation Respiratory distress Planned thymectomy
Patient 2						
Pregnancy 1	nil	39	LSCS for pathological	3500	nil	Nil

			CTG			
Pregnancy 2	nil	37	Forceps delivery	3560	TNMG	Nil
Patient 3						
Pregnancy 1	nil	39	Vaginal	2900	nil	nil
Pregnancy 2	nil	36	Twin Vaginal delivery	2100 2300	nil	nil
Pregnancy 3	Exacerbation in the third trimester	38	Vaginal	2390	nil	Puerperal sterilisation done
Patient 4						
Pregnancy 1	Nil	39	LSCS for fetal bradycardia	2800	nil	Exacerbation one month postnatally Underwent thymectomy
Pregnancy 2	Exacerbation in third trimester	39	Elective LSCS and sterilisation	3040	TNMG	nil
Patient 5	Exacerbation in second trimester	38	Vaginal delivery	2210	nil	nil
Patient 6						
Pregnancy 1	Abortion at 20 weeks					
Pregnancy 2	Exacerbation in third trimester	38	Vacuum delivery	2530	nil	nil
Patient 7						
Pregnancy 1	Nil	39	LSCS for failed induction	2750	nil	nil
Pregnancy	Nil	40	Elective	2650	nil	nil

2			LSCS			
Pregnancy 3	Nil	39	Elective LSCS and sterilisation	2480	nil	nil

GA- Gestational age CTG- Cardiotocogram TNMG- Transient neonatal myasthenia gravis LSCS- Lower segment caesarean section

Table 3: Myasthenia gravis in pregnancy: A review of the literature

Reference	Number of pregnancies studied	Disease exacerbation	Cesarean rate	Neonatal myasthenia	Adverse outcomes	Other inferences
Plauche 1991[8]	322	41% relapse 29.8% exacerbation in puerperium	13.5%	16.1%		
Batocchi, 1999[9]	64	17% on no treatment and 19% on treatment	30%	9%		
Djelmis, 2001[4]	69	15% in pregnancy 16% in puerperium	17%	30%	1 abortion	
Hoff 2003[5]	127		17.3% vs 8.6% in control group with no MG	5	Higher complication rate at delivery- 40.9% vs. 32.9%. and thrice higher risk of	Five neonates with severe anomalies. 3 neonatal deaths- all had skeletal anomalies (could

					PPROM (5.5% vs 1.7%)	represent arthrogryposis)
Hoff, 2007[10]	135	10%	44.8%	19%	16% abortion,21% -antenatal complications (preeclampsia , PROM) 30% intrapartum complications (protracted labour, PPH, etc.)	Risk of neonatal myasthenia halved following thymectomy
J C Wen, 2009[11]	163	-	44.8% vs 37.4% OR 1.33 (95%CI =0.94-1.88)		6.8% LBW vs 5.6% in controls 17.8% SGA vs 14.1% in control 8.1% PTB vs 8.1% in control	No statistically significant difference in the risk of preterm, LBW, SGA and cesarean between MG and non-MG group
Almeida C, 2010[12]	17	4 during pregnancy	8 cesarean	none	2 first trimester abortions	Loco regional anaesthesia (Mainly epidural) is preferred
Antonio Costa	30	56.7% overall	64.3%	2 neonates	6.7% miscarriage	

Braga, 2016 [13]		43.3% in pregnancy			rate No IUGR, PTB, PE or IUD	
Ducci, 2017[14]	35	50% mainly in the second trimester	66.7%	12.9%	25.8%- PPROM Abortion- 11.4% Fetal death- 2.9%	
Current study	14	3 antenatally 1 postnatally	7 (50%)	2 neonates	1second trimester abortion	Two underwent pre-pregnancy thymectomy and both had exacerbations

Abbreviation: PPROM- Preterm premature rupture of membranes, PROM- Prelabour rupture of membranes, PPH- postpartum haemorrhage, LBW- low birth weight, SGA- Small for gestational age IUGR- intrauterine growth restriction, PTB- preterm birth, PE- preeclampsia, IUD- intrauterine fetal death