SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
THIRUVANANTHAPURAM, KERALA

A RETROSPECTIVE STUDY ON PREGNANCY IN MYASTHENIA GRAVIS

Thesis submitted in partial fulfilment of the rules and regulations for

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DECLARATION

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SYNOPSIS

Myasthenia gravis is an autoimmune antibody mediated disease affecting neuromuscular junction. The course of myasthenia in pregnancy is unpredictable and the data describing the effect of disease and treatment modalities on pregnancy, labour and neonatal outcomes is limited, especially from India.

This study is a hospital based retrospective chart analysis about the effect of pregnancy on course on myasthenia gravis and the effect of myasthenia and its treatment on pregnancy, delivery and neonatal outcomes. We studied 17 pregnancies of 15 subjects among the 227 females from 13 to 55 years age diagnosed as myasthenia over a period from 1999 till 2018 in SCTIMST. Data was extracted from previous hospital records, obstetric records, and directly from patient through a questionnaire. The change in MGFA score was compared between prepregnancy, 1st, 2nd and 3rd trimesters and postpartum period and change in clinical status was coded as deterioration, no change, remission or improvement.

One third of patients had ocular myasthenia at onset. Fifty three percent were AchR antibody and 2% were MuSK antibody positive. In the prepregnancy stage, all subjects had mild weakness indicated by a class I or class II MGFA score. There was a deterioration in MGFA score predominantly in the postpartum period (in 4 pregnancies) followed by a worsening in 2 pregnancies in 2nd trimester and 1 pregnancy in 1st trimester. About 86% of subjects were on pyridostigmine, 52% were on oral steroids and 26% on azathioprine during first trimester of pregnancy and 43% were on all the three medications together. Regarding pregnancy outcome, 3 pregnancies had abortions; 2 spontaneous and 1 induced abortion and 2 subjects with spontaneous abortions were on immunomodulation with steroids and azathioprine and also on cholinesterase inhibitors. 42.9 % pregnancies were delivered by Caesarian section and among the eight spontaneous deliveries, one was assisted delivery and one was preterm delivery. Fetal outcome

analysis showed poor APGAR scores in two neonates and presumed typical transient neonatal myasthenia gravis in 2 babies and there were no congenital anomalies.

The clinical course of myasthenia is generally unchanged during pregnancy with deterioration predominantly occuring in the postpartum period. Adequate treatment and monitoring may be helpful in preventing life threatening exacerbations. Myasthenia could have an unfavourable outcome on pregnancy like spontaneous abortions or premature rupture of membranes. Transient neonatal myasthenia is a concern but has a good prognosis. No adverse effects to medictions or any congenital anomalies were noticed in our study.

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INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease affecting the postsynaptic membrane at the neuromuscular junction (NMJ) with fatiguable muscle weakness as the predominant symptom (1). The disorder is characterized by a decrease of the number of acetylcholine receptors in the neuromuscular plates, due to autoantibodies. Muscles innervated by cranial nerves especially oculofacial and bulbar muscles are commonly affected although generalised muscle weakness can be a presenting feature (2). The disease is two times frequent in women than in men, and young women especially in the childbearing age group are typically affected and has an impact on pregnancy also (3). During pregnancy, in one third of patients, the disease exacerbates, whereas in two thirds no change is present. Worsening commonly occurs in the first trimester or in the immediate post partum period (4).

Treatment is based on subgroup classification and modalities include acetylcholinestease inhibitors, thymectomy and immunotherapy. Intravenous immunoglobulin and plasma exchange are used for acute exacerbations and intensive care is necessary during exacerbations with respiratory and bulbar failure. Eventhough the clinical course and pathophysiology are well studied, comorbidities and the impact on quality of life are significant.

Signs and symptoms of MG in pregnant women tend to improve during the second and third trimesters and complete remission can occur in some patients. The outcome of earlier pregnancies does not help in predicting the course of the current pregnancy or the future ones. The disease is not associated with sterility, but a noticeably higher incidence of spontaneous abortions is observed in the myasthenia patients. Limited data are available on the increased incidence of premature labors or preeclampsia in pregnant women suffering from MG. Neonatal complications are also noticed after delivery which requires prompt identification and management. Treatment is frequently necessary before, during, and after pregnancy to ensure maternal and fetal well-being and the challenges posed being the exacerbations and adverse effects of medications on fetus (5) (6). However, knowledge of the potential effects of the pregnancy on

the course of MG and the use of immunosuppressive (IS) drugs during pregnancy is limited, making it difficult for both clinicians and patients to optimise medications. This study is to evaluate the effect of pregnancy on the course of myasthenia gravis, the effect of myasthenia gravis on the course of pregnancy, on delivery and neonatal outcomes and also the influence of drugs for myasthenia on pregnancy outcomes. A comprehensive interdisciplinary approach is needed in pregnant patients with myasthenia including neurologist, obstetrician and neonatologist so that optimal patient care is ensured (7).

REVIEW OF LITERATURE

BRIEF HISTORY OF MYASTHENIA GRAVIS

Thomas Willis first described a patient in 1672 with fluctuating limb and bulbar weakness. Jolly described one patient in 1895 who presented with fatiguable weakness improved after taking some rest and proposed the name "myasthenia gravis pseudoparalytica". Neostigmine was first used in 1935 to treat myasthenia gravis (8). Acetylchoine receptor antibodies were first identified by Lindstorm and colleagues in 1976 (9). Blalock in 1939 reported remission of myasthenia gravis in 21 year old patient following thymectomy (10).

EPIDEMIOLOGY AND RISK FACTORS

The overall prevalence of MG is 150–250 cases per million population and estimated annual incidence is 8–10 cases per million person-years(3) (11).The prevalence and incidence of each subgroup of MG vary markedly, partly owing to variation in demographics between countries (12). The age at onset of AChR MG has a bimodal pattern, with a lower peak at 30 years of age and a higher peak at 70–80 years of age (12). In India,however disease was more common in males (M:F ratio of 2.7:1) and had single peak of age at onset with males sixth to seventh decade in males and third decade in females (13).

Both predisposing genetic factors and environmental factors contribute to the induction of MG (14). *HLA* genes, *PTPN22, CTLA4, IL1B, IL10, TNF, IFNG, CD86, AKAP12, VAV1, TNFSF13B* (also known as *BAFF*) and *TNIP1* are some of the contributory genes.

The treatment of MG has improved over time and life expectancy is near normal in developed countries, whereas MG had a raised mortality until a few decades ago (15) (16). A relative mortality of 1.41 was demonstrated for AChR MG in individuals diagnosed between 1985 and 2005 in a study in Denmark (16).

Sex hormones have a role in disease predisposition and might explain the different sex ratio in early onset and late onset MG and the higher frequency of MG among young women and postpartum (17) (3). Early onset MG is thrice common in females whereas late onset MG is slightly more common in males. Thymic hyperplasia also primarily affects young females suggesting the role of hormones in MG pathogenesis and have implications in treatment modalities like thymectomy (18). Oestrogens have influence anti-inflammatory and pro-inflammatory responses, depending on their dose, timing and the microenvironment (19). Sex hormones affect the expression of thymic transcription factors such as autoimmunie regulator (AIRE) and augment the risk of developing MG with AChR antibodies (20).

PATHOGENESIS

MG is one of the most studied autoimmune disease. MG is an antibody mediated autoimmune disease with T cells having intermediary role. The associated autoantibodies can be classified into two major groups: those to transmembrane or extracellular autoantigens and those to intracellular autoantigens.

Antibodies to transmembrane or extracellular proteins

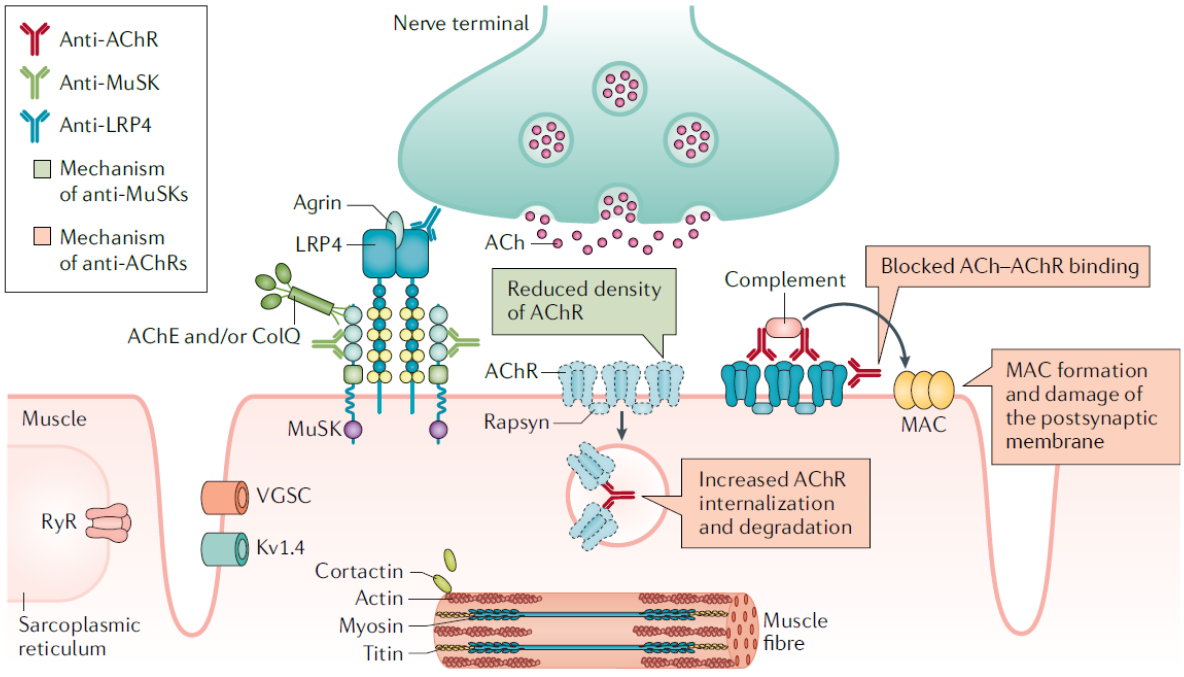
These could be either directly (such as anti-AChR antibodies) or indirectly (such as anti-MuSK antibodies and anti-LRP4 antibodies) acting. Anti-AChR antibodies are detected in 80% of patients with MG (1). Mechanism for the pathogenetic effect of anti-AChR antibodies could be either due to a) complement activation or b) antigenic modulation which causes acceleration of AChR internalization and destruction mediated by the crosslinking of AChRs by bivalent antibodies and thus reduced postsynaptic receptor concentration (21). Antibodies targetting the AchR α-subunit are more pathogenetic for MG than antibodies that target other AChR subunits, and their epitope pattern influences disease severity (22).

MuSK is activated through phosphorylation induced by the LRP4–agrin complex, following which AChR clustering occurs and proteins like rapsyn play a role. Anti-MuSK antibodies are identified in 1–10% of patients with MG and they belong to the IgG4 subclass, they could not activate complement and could not induce antigenic modulation because of their monovalent nature(23).

Other antibodies to extracellular proteins include LRP 4, Agrin, Col Q and Kv 1.4 and the exact pathogenetic basis of their mechanisms are still evolving (2).

Antibodies against intracellular antigens are unlikely to be pathogeneic but have utility as markers of disease severity, presence of thymoma and myopathy, particularly anti titin antibodies. Other antibodies to intracellular proteins include antibodies to ryanodine receptor and cortactin (2).

Figure 1. Neuromuscular junction anatomy and various autoantibodies and their binding sites (2)



Adapted from Gilhus et al., Myasthenia gravis. Nat Rev Dis Primers. 2019 Dec;5(1):30

ROLE OF THYMUS AND T CELLS

The thymus is affected commonly in patients with AChR MG. Thymoma is seen in 10% of patients or thymic follicular hyperplasia seen in >80% of patients with early-onset MG (18). Up to 30% of thymoma patients have myasthenia gravis (24). Type B2 WHO histological grade is most commonly associated with MG, followed by types AB and B1 (25). All thymomatous MG patients are ususally positive for anti-AChR antibodies, and this underlines the role of thymus in the initiation of the autoantibodies (26). Thymectomy produces considerable improvement in patients (27).

The presence of many germinal centres with anti AchR antibody producing B cells in the thymus seen in Thymic hyperplasia suggests that the thymus is the site where loss of immune tolerance to AchR occurs (28). CD8 positive (CD8+) T cells which escape the central tolerance mechanisms in thymus are important players during the initiation of MG. The tumour induces the loss of tolerance to AchR.

CLINICAL FEATURES

Fluctuating fatiguable weakness which is aggravated by exertion and alleviated by rest is the cardinal feature of MG. Weakness is accentuated by bright sunlight, surgery, emotional stress and intercurrent illness (eg, bacterial and viral infection), medications (eg, aminoglycosides, ciprofloxacin, chloroquine, procaine, lithium, phenytoin, beta- blockers, procainamide, statins) (29). The common differentials include congenital myasthenic syndromes especially the slow channel, *ColQ* or *DOK7* syndromes where a worsening with pyridostigmine is seen and Lambert Eaton Myasthenic syndrome with antibodies against presynaptic voltage gated calcium channels seen in >90% of LEMS patients and 60% of LEMS patients have associated malignancy, usually small cell lung carcinoma (30).

Myasthenic weakness commonly involves ocular, bulbar, proximal limb and neck muscles, and in a few patients involves respiratory muscles also. Around one third of MG patients presents with mild weakness, another one third with moderate weakness, and rest have severe weakness often associated with bulbar symptoms. Around 85% patients present initially with ocular muscle weakness with diplopia, blurring of vision, fluctuating ptosis and among them half will develop generalised progression over next two years. Bulbar involvement during the clinical course may be seen in up to 60% of the patients, and fatiguable chewing difficulty more for solid food, with preferential involvement of jaw closure than jaw opening is seen (31) (32). Around 15 % of patients present with painless dysphagia and dysarthria. Respiratory muscles involvement is less common in the first 2 years and it may be the the presenting feature in rare cases (33).

Myasthenic crisis is a life threatening exacerbation because of respiratory muscle involvement, requiring ryles tube feeding and mechanical ventilation. Patients with MG can present with predominantly proximal muscle weakness in upper and lower limbs, with preferential involvement of upper limbs in MG differentiating it from myopathy. Facial muscle involvement may give an expressionless appearance.

CLASSIFICATION OF MYASTHENIA GRAVIS SUBGROUPS (17)

- **Early onset MG**: AChR Ab positive, usually seen in <50 years of age and thymic hyperplasia is more common in this subgroup
- **Late onset MG**: AchR Ab positive, seen in >50 years of age with Thymic atrophy commonly present
- **Thymoma MG**: AchR Ab positive, may occur in any age group, Thymus show Type AB and B thymoma
- **MuSK MG**: MuSK Ab positive, may occur in any age group and usually no Thymoma is seen

- **LRP4 MG**: LRP4 Ab positive and no thymoma
- **Seronegative MG**: No positive antibodies are detected
- **Ocular MG**

MGFA Clinical Classification (34)

Class I: Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.

Class II: Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.

B. IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class III: Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.

B. IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class IV: Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.

B. IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class V: Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

DIAGNOSIS

Electrophysiology:

RNS (repitative nerve stimulation study) and SFEMG (single fiber electromyography) are most commonly used electrophysiological test for the diagnosisis of MG. 10% decremenal response between the first and the fifth evoked compound motor action potential is taken as positive RNS and is diagnostic of MG.Around 75% of patients with generalised MG and 50% of patients with ocular MG show positive RNS study (35).

SFEMG is the most sensitive method to diagnose MG, records action potentials of two skeletal muscle fibers innervated by the same motor axon. SFEMG records the jitter, which is defined as difference in time of the second action potential relative to the first action potential. In MG due to decrease in AchR over muscle endplate safety factor of transmission is reduced, results in increase in jitter. 95%–99% of patients with generalised Myasthenia gravis show jitter on affected muscle (35).

Ice pack test: It is a simple bedside test, baseline ptosis is recorded and then ice pack is placed over the eye for 2–5 minutes and then reassessed for improvement in ptosis.

Neostigmine Test: Neostigmine is a short-acting acetylcholinesterase inhibitor which is administered intravenously and the patient is observed for objective improvement in muscle strength particularly the ptosis.

Management of MG

Strategies include:

(i) Symptomatic treatment by using Acetylcholinesterase inhibitors like Neostigmine and Pyridostigmine

(ii) Short-term immunomodulation with intravenous immunoglobulin and plasmapheresis

(iii) Long-term immunomodulation with steroids and other immunosuppressants

Surgical treatment-Thymectomy

PREGNANACY AND MYASTHENIA GRAVIS

Maternal changes in pregnancy can affect an autoimmune disease, vice versa the disease can also affect the outcome of pregnancy and the child.The effect of female sex hormones on thymic involution was discussed previously (18) (19).

Exacerbations are unpredictable in preexisting disease and not unusual during pregnancy, labor, or the postpartum period.Underlying infections especially in the postpartum period pose a major risk factor for exacerbations (36). Eventhough an uneventful course and a good outcome is possible in pregnant women who have MG, there are many challenges requiring special clinical consideration and coordinated care between multiple disciplines are needed (37).

TREATMENT OF MYASTHENIA GRAVIS DURING PREGNANCY

The treatment strategies should be individualised based on subgroup classification.Severe disease with bulbar and respiratory muscle involvement should be treated aggressively.Thymectomy should be preferably done before planning pregnancy or after

postpartum period (37). MG patients with thymoma who have not undergone thymectomy have a higher incidence of exacerbation than those who have undergone thymectomy(38) (39). Infants born to MG patients who have undergone thymectomy have reduced risk of developing neonatal myasthenia gravis.

Pyridostigmine is generally safe in pregnancy and lactation and there are no teratogenic effects reported till now (40). Dose adjustment is required in pregnancy as a result of increased renal clearance, expanded maternal blood volume, delayed gastric emptying and emesis.

Prednisolone and azathioprine are safe during pregnancy and breastfeeding whereas methotrexate, mycophenolate mofetil and cyclophosphamide are teratogenic and should be avoided in women of child bearing age (6). Rituximab preferably should be stopped 6 months before a planned pregnancy in women with MG. Intravenous immunoglobulins and plasma exchange are safe during pregnancy.

EFFECT OF PREGNANCY ON THE COURSE OF MYASTHENIA GRAVIS

Pregnancy has an unpredictable effect on course of MG.Each pregnancy has a different effect on disease course and hence doesnot predict course of future pregnancies.One third of pregnant patients experience worsening of MG, commonly in first trimester and 3 months postpartum (41).The maximum risk of mortality is seen in the first year after onset of disease.Improvement occurs in one third women in second and third trimester probably due to physiological immunosuppression with rare reports of complete remission.Disease severity before conception doesnot predict the clinical course (42).

EFFECT OF MYASTHENIA GRAVIS ON LABOUR AND DELIVERY

Smooth muscle involvement alone in the first stage of labour poses no challenge**.** Involvement of skeletal muscle in the second phase of labour is concerning during

delivery. Elective Caesarian section may even cause sudden worsening. Generally vaginal delivery is favoured with use of pyridostigmine and steroids if needed. Magnesium sulphate used for eclampsia and non depolarising muscle relaxants used for anaesthesia may worsen myasthenic symptoms. Previous studies show an overall increased rate of delivery complications and a higher rate of intervention during delivery with premature rupture of the membranes being the only single complication without any significantly incraesed perinatal mortality and a mildly increased risk of congenital defects (38).

PREGNANCY AND ANTI MUSK MYASTHENIA

AntiMuSK antibodies seen commonly in females, is negative in anti AChR antibody positive MG patients. MuSK MG presents with prominent bulbar, neck, shoulder girdle and respiratory weakness. They are IgG class 4, and their placental transfer is poorer than that for anti AChR antibodies, which are IgG1 and IgG3. Hence the chance of developing anti MuSK antibodies in transient neonatal myasthenia gravis is low, but it is possible to transmit anti MuSK antibodies from the umbilical cord to the newborn. Mothers and infants needs to be monitored carefully especially for nutritional deficiencies and hydramnios, and plasmapheresis should be carried out without delay in cases of bulbar involvement (43).

EFFECT OF MATERNAL MYASTHENIA ON NEONATE

TRANSIENT NEONATAL MYASTHENIA GRAVIS (TNMG)

Transient neonatal myasthenia gravis affects 10% to 20% of newborns of myasthenic mothers and occurs immediately after birth (41) (44). Symptoms develop within 1-2 days after birth and include generalized weakness and difficulty feeding, hypotonia, poor cry, ptosis, facial paralysis, and respiratory distress. The transfer of water soluble anticholinesterase medications

from the mother to the newborn and Alfa feto protein (AFP) causes delayed occurrence of TNMG. AFP has a protective role due to its powerful inhibitory effect on the AChR Ab binding capacity (45). The clinical improvement or remission seen in myasthenic mothers during the later trimesters could be the result of the elevated levels of AFP in maternal serum from increasing placental permeability to fetal placental proteins that occurs with advancing gestation. TNMG symptoms vary between mild to severe at times requiring ventilatory assistance. The syndrome usually resolves within 1-4 months. NMG symptoms respond to anticholinesterase medications and improve progressively with a reduction in the antibody titres.

Plasmapheresis may be helpful in very severe cases. NMG is caused by transplacental passive transfer of circulating nicotinic AChR Abs from the mother to the fetus. Thus higher antibody titres in mother may predict severity of TNMG. But there are cases of myasthenic mothers who do no have detectable AChR antibodies and have had babies who have NMG are also reported (46). There is no correlation between severity of maternal MG symptoms with the severity of NMG in the newborn, and NMG can even occur in infants of mothers who are in clinical remission. A high ratio of antiembryonic AChR to antiadult muscle AChR Abs correlates with the occurrence of NMG and could be having a pathogenic role (47).

ARTHROGRYPOSIS

Arthrogryposis multiplex congenita (AMC) may be caused by placental transfer of antibodies against the fetal AChR in some infants born to myasthenic women. Nonprogressive multiple congenital joint contractures developing in utero from lack of fetal movements, preventing normal joint formation is the major feature. This rare condition may lead to intrauterine death or neonatal death attributed to associated pulmonary hypoplasia and polyhydramnios (48) (49). Prenatal Ultrasound may be helpful in detecting this condition. A complex phenotype of

dysmorphic facies, abnormal genitalia, central nervous system atrophy, and lung hypoplasia also has been reported in a neonate born with arthrogryposis.

LACTATION

Pyridostigmine is considered safe during lactation. Azathioprine and its metabolites have been found in breast milk, exposing the child to 0.1% of the maternal dose. The American Academy of Pediatrics does not recommend breastfeeding because of the risk of immunosuppression, carcinogenesis and growth restriction in the child (50). However many reports suggest that use may be safe in pregnancy and breast feeding (51). Prednisolone is the preferred corticosteroid;it is metabolized by the placenta, and just 10% crosses into the fetal circulation at doses of less than 20 mg (52). Discarding breast milk for the first 4 h after ingestion of a dose of prednisolone ≥20 mg may be a safer practice to avoid neonatal adrenal suppression.Methotrexate, cyclosporine and tacrolimus are not advised during either pregnancy or breastfeeding (50).

GOAL AND OBJECTIVES OF THE STUDY

Study Goal

The study intends to learn the effect of pregnancy on the course of MG, effect of MG on pregnancy outcome and influence of drugs for MG on pregnancy outcome so that it may help clinicians to decide regarding optimal treatment of the disease during pregnancy and early identification of fetal and neonatal issues in mothers having MG.

Objectives of the study

- To study the effect of pregnancy on the course of myasthenia gravis
- To study the effect of myasthenia gravis on the course of pregnancy, and pregnancy and neonatal outcomes
- To study the influence of drugs for myasthenia in pregnancy and neonatal outcomes

Materials and methods

Study setting and population:

This study is a hospital based retrospective cross-sectional study.

The subjects were recruited from patients previously admitted in the Neurology wards or attending the Neuromuscular Clinic of Sree Chitra Tirunal Institute for Medical Sciences and Technology.

All females either outpatient or inpatient diagnosed as Myasthenia gravis fulfilling the inclusion and exclusion criteria in SCTIMST from a period of January 1, 1999 to December 31,2018 will be recruited. All the patients were recruited after obtaining informed consent.

Eligibility Criteria:

Criteria to recruit under study are:

Inclusion criteria-

1) Female sex
2) History of pregnancy after or concurrent with diagnosis of MG

3) Myasthenia gravis diagnosed by criteria-

Fatiguable weakness plus one of the following

a) AchR Ab or MusK Ab positivity

b) RNS/SFEMG positivity

c) Neostigmine test positivity

Exclusion criteria:

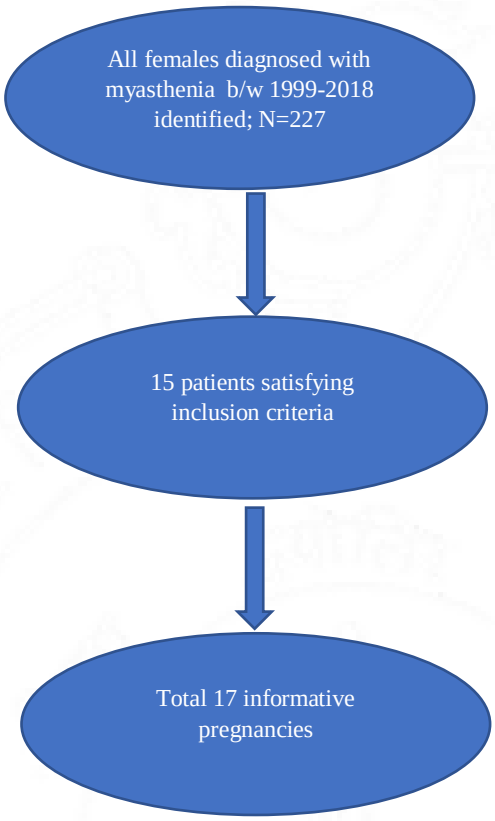
1) Congenital Myasthenic syndrome

2) Alternate differential diagnoses not satisfactorily excluded

3) Patient with possible pregnancy not available for visit

4) Patients with incomplete hospital records

Figure 2. Selection process of subjects



Data Collection Procedures

Selection of subjects:

The subjects were recruited from female patients previously admitted in the Neurology wards or visiting the Neuromuscular Clinic of Sree Chitra Tirunal Institute for Medical Sciences and Technology with a diagnosis of Myasthenia gravis. The patient was considered to fulfil the criteria for diagnosis of Myasthenia gravis if she has a

Fatiguable weakness plus one of the following:

a) AchR Ab or MusK Ab positivity

b) RNS/SFEMG positivity

c) Neostigmine test positivity

All female patients with disease onset in the age group of 13-55 years were identified and were contacted through phone or post. Patients with informative pregnancy who are on regular follow up from Neuromuscular clinic were given a structured questionnaire and data was extracted.

Patients with Informative pregnancy means:

- Diagnosis of MG prior to pregnancy or
- Diagnosis of MG established during pregnancy or within 6 months postpartum

Data collection was done through:

1) Structured questionnaire

2) Either in person or by phone

3) From the hospital records

The demographic and contact information of the subjects were collected. The clinical data, antibody status and current treatment details of the patients were extracted from their hospital records using a structured proforma. The data on the non-serologicaltests investigations used for diagnosis MG were also specifically recorded –neostigmine test, ice pack test, RNS and CT thorax for thymic status. These tests were recorded only if they are already done and were not done for the purpose of the study.

Data regarding exacerbations and remissions of the disease during the three trimesters and post partum period compared to status of patient 1 year prior to pregnancy were collected from previous hospital records. Clinical classification using MGFA score from was done. Based on MGFA status, it was coded as

1) Remission

2) Improvement

3) No change

4) Deterioration

The effect of Myasthenia on pregnancy was assessed by collecting data on

a) Coexisting medical conditions

b) Fetal outcome – Abortions, IUD, stillbirth

c) Mode of delivery – vaginal spontaneous or vaginal forceps associated or Caesarian section.

The data on Neonatal outcomes like a) birth weight b) infections c) Prolonged hospitalization d) Transient Neonatal Myasthenia Gravis e) ICU requirement and f) any congenital diseases, were collected from previous hospital records.

Data regarding other variables like medication status in the one year before pregnancy and during pregnancy and status of thymectomy at the onset of pregnancy was also collected.

The study did not involve HIV testing, collection of blood or other biological samples or genetic testing.

Statistical analysis

Descriptive statistics were expressed as means (standard deviation) and proportions. Mean MGFA ranks across stages were compared using nonparametric Friedman test. Wilcoxon Signed Rank test was used to do a pairwise comparison of MGFA scores in various stages. All statistical analysis were done using SPSS software.

Ethical considerations

This study has the approval of the Institutional Ethics Committee (IEC Regn No.1347/2019) and informed consent was obtained from all subjects.

RESULTS

All female patients with disease onset in the age group of 13-55 years who were admitted or on OPD followup from SCTIMST between 1999 and 2018 were identified. A total of 227 female Myasthenia gravis patients were identified and among them there were total 15 patients who had diagnosis of MG prior to pregnancy or diagnosis of MG established during pregnancy or within 6 months postpartum, were recruited for the study. In total there were 17 informative pregnancies.

PATIENT PROFILE AND DISEASE CHARACTERISTICS

DEMOGRAPHIC PROFILE OF PATIENTS

The mean age of subjects at recruitment was 31.1 ± 6.4 years with a minimum age of 21 years and maximum age of 41 years. Around 60 % of subjects were graduates.

Table 1. Age group distribution of patients

Age group	Frequency	Percent
15-25 years	3	20.0
26-35 years	8	53.3
36-45 years	4	26.7
Total	15	100

Mean age of onset of Myasthenic symptoms was 21.4 ± 5.7 years with minimum age of onset 13 years and maximum age of onset 29 years. The mean interval between disease onset and pregnancy was 3.7 ± 3 years.

The mean age of pregnancy was 25.5 ± 3.8 years with minimum and maximum ages of conception 19 and 31 years respectively. Out of the 17 informative pregnancies, 1 patient had onset of symptoms at 3 months postpartum period. One patient had onset of disease 1 month prior to pregnancy. One patient was in clinically stable remission for 3 years before pregnancy and was remaining in remission till postpartum.

Table 2. Mean age of onset of disease and mean age of pregnancy

	N	Mean ± SD (years)	Range Min- Max (years)	Median	IQR
Age of onset of symptoms	15	21.4 ± 5.7	13 - 29	24.0	15 - 26
Interval b/w symp onset and pregnancy	17	3.7 ± 3	0-9	4.0	0.6 -6.5
Age of pregnancy	17	25.5 ± 3.8	19-31	27.0	21.5-28.5

DISEASE CHARACTERISTICS

At the onset of symptoms, 35.3% subjects had purely ocular symptoms. One patient went into clinically stable drug free remission 1 year after the onset and after thymectomy. Among the rest, none of the patients were in pharmacological remission. As indicated by the MGFA status at onset, none of the patients had moderate or severe weakness. 35.3% pregnancies had class I MGFA at onset of disease and 64.7% had class II MGFA at the onset of disease. The mean duration from symptom onset to pregnancy was 3.7± 3 years. None of the patients had any associated comorbidities like thyroid dysfunction or diabetes.

Four subjects had Neostigmine test positive, 6 subjects had icepack test positive, 10 had AchR antibody positive and 12 subjects had RNS positive. Two patients who were AchR Ab negative and RNS positive had MuSK Ab detected on later followup. In the whole group, 7 out of 15 subjects were AchR antibody negative.

Out of the 17 pregnancies, 7 patients had suspected thymoma detected by CT thorax. All the 7 patients underwent thymectomy, 6 underwent before pregnancy and 1 patient who had postpartum onset of symptoms underwent after delivery. Histopathology showed thymoma in 4 (57.1%), thymic hyperplasia in 2 (28.6%) and involuted thymus in 1(14.3%) pregnancies.

Regarding treatment, 11 patients were on oral prednisolone from the onset, 4 patients were initiated on Azathioprine and 16 patients were on pyridostigmine.

Table 3. Frequency of symptoms at onset

Symptoms at onset	Frequency	Percent (%)
Bulbar	2	11.8
Bulbar + ocular	2	11.8
Ocular	6	35.3
Ocular + Limb weakness	1	5.9
Ocular + Limb weakness+ Bulbar	3	17.6
Pure limb weakness	3	17.6
Total	17	100

Figure 3. Frequency of symptoms at onset

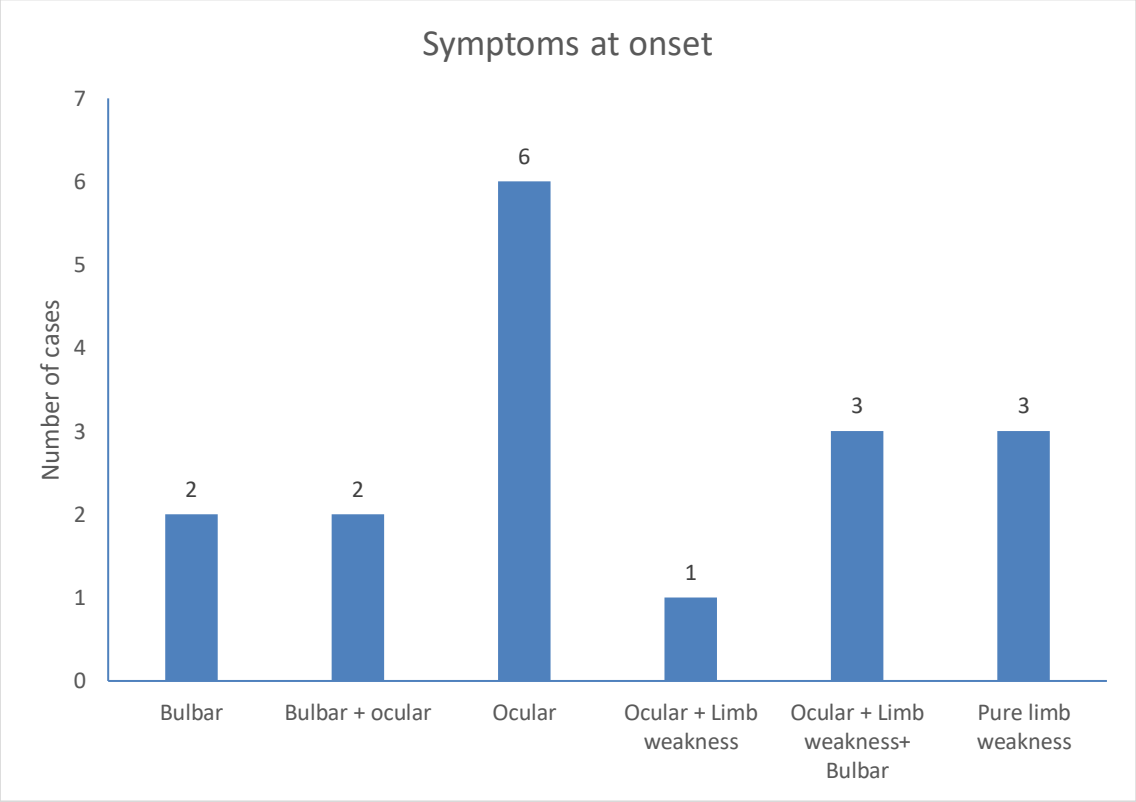


Figure 4. Frequency of positive diagnostic tests

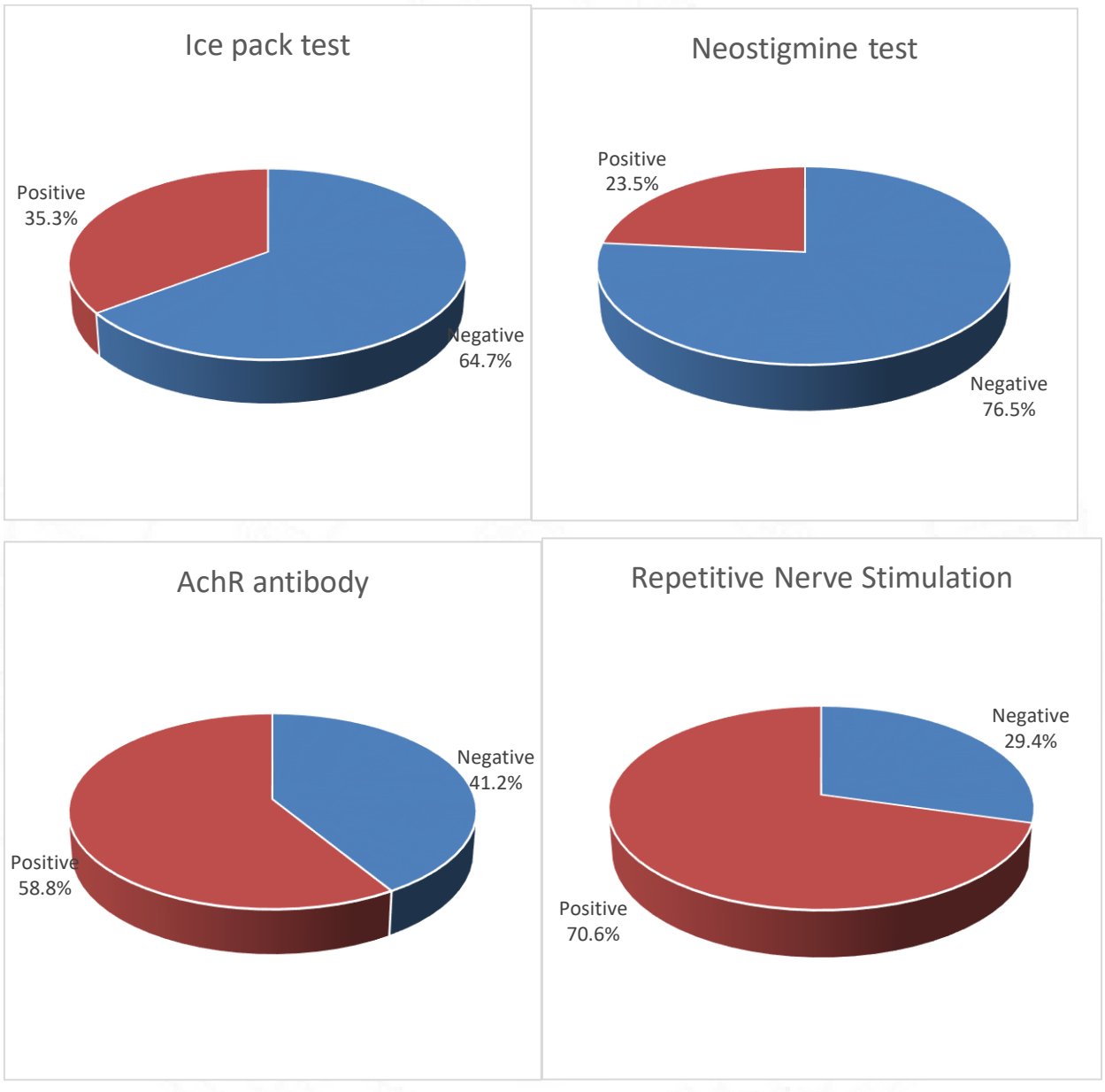


Figure 5. Frequency of combined positive diagnostic tests

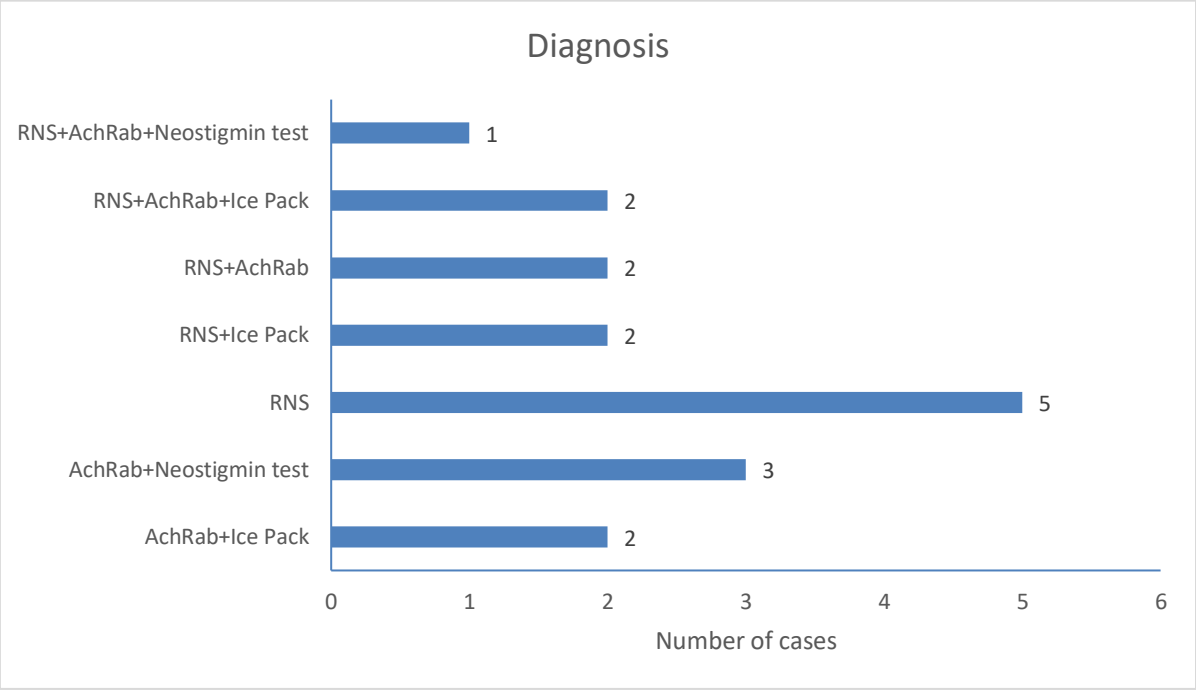


Figure 6. Proportion of MGFA classes at the onset of symptoms

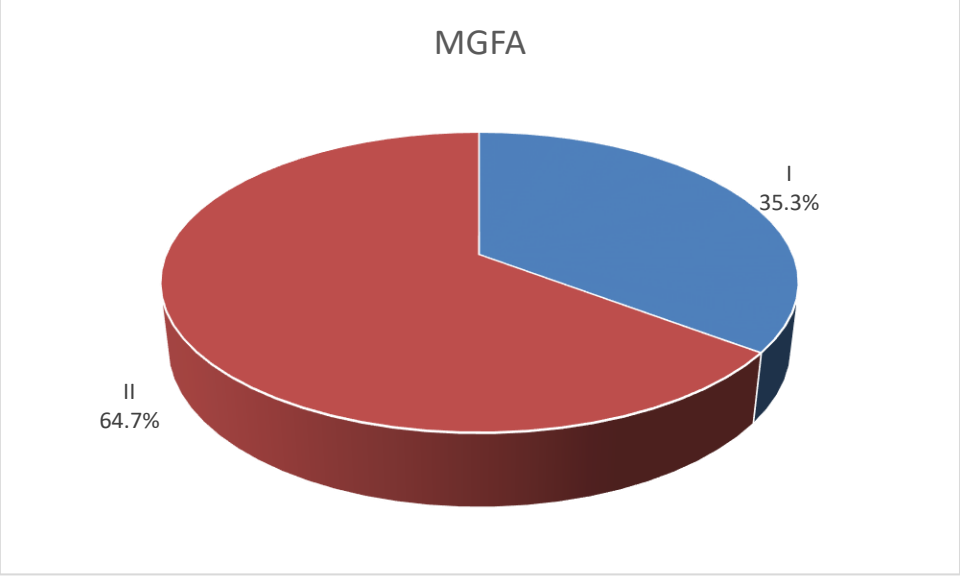


Figure 7. Proportion of thymoma in CT thorax

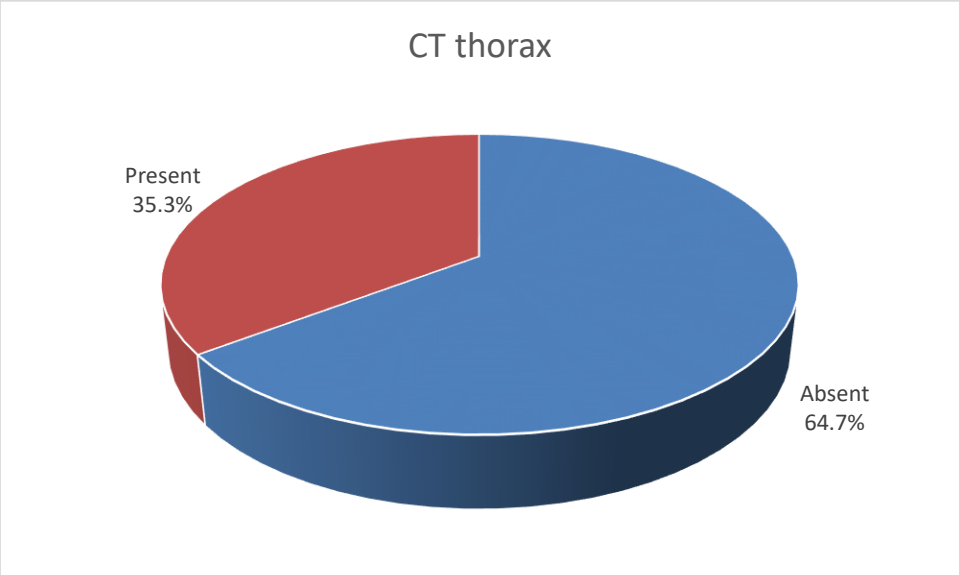


Figure 8. Proportion of Thymoma in histopathological examination

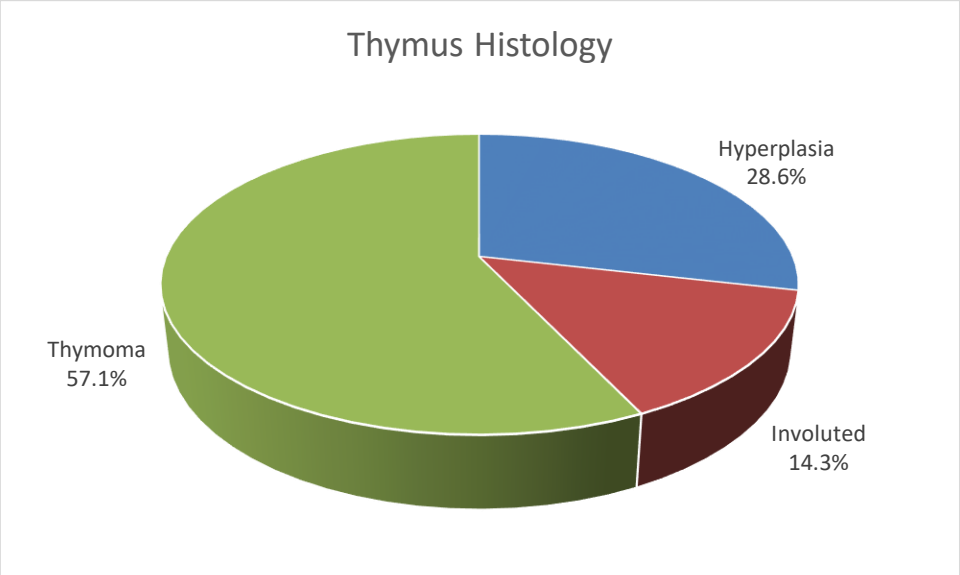


Figure 9. Age group distribution of Thymectomy

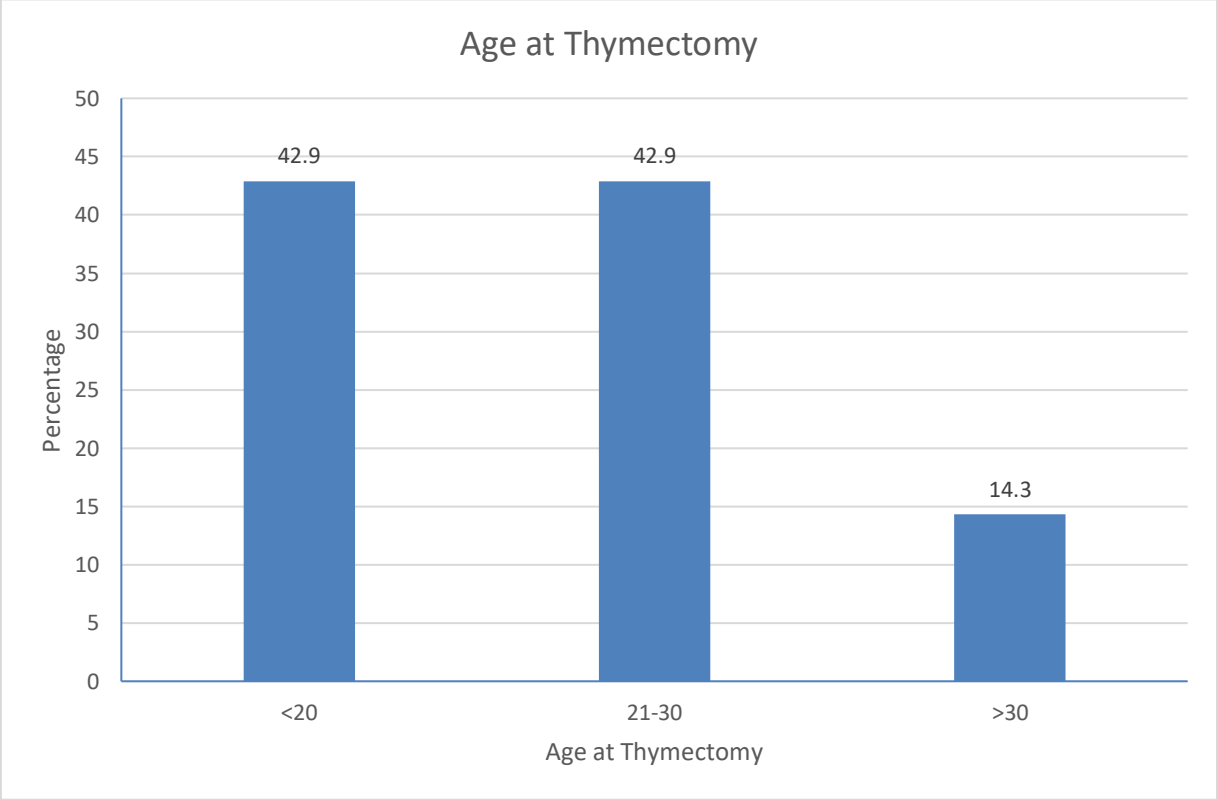


Table 4. Patient profile and disease characteristics

	Age at onset (years)	Type of MG	Ab status	Thymoma/ Thymectomy	Treatment received	MGFA at onset
P1	29	Generalised	AchR Ab	Yes/Yes	Steroid	II
P2	5	Generalised	Negative	Yes/Yes	Steroid Azathioprine Pyridostigmine	II
P3	3	Generalised	MuSK Ab (on followup)	No	Steroid Pyridostigmine	II
P4	24	Generalised	AchR Ab	No/Yes	Steroid Azathioprine Pyridostigmine	II
P5	26	Ocular	AchR Ab	Yes/Yes	Pyridostigmine	I
P6	19	Generalised	MuSK Ab (on followup)	No	Steroid Azathioprine Pyridostigmine	II
P7	27	Ocular	AchR Ab	No	Steroid Pyridostigmine	I
P8	25	Generalised	AchR Ab	No	Steroid Pyridostigmine	II
P9	24	Ocular	AchR Ab	No	Steroid Pyridostigmine	I
P10	15	Generalised	Negative	No/Yes	Steroid Azathioprine Pyridostigmine	II
P11	13	Ocular	AchR Ab	No	Steroid Pyridostigmine	I
P12	26	Ocular	Negative	Yes/Yes	Pyridostigmine	I
P13	15	Generalised	AchR Ab	No	Pyridostigmine	II
P14	29	Generalised	Negative	No	Pyridostigmine	II
P15	19	Ocular	Negative	No/Yes	Steroid Pyridostigmine	I

COURSE OF MYASTHENIA GRAVIS IN PREGNANCY

Of the 17 total pregnancies, 15 (88.2%) were 1st time pregnancies, 1 (5.9%) was 2nd pregnancy and 1 (5.9%) was 3rd pregnancy.

We coded various stages as T0-3 months prepregnancy, T1- 1st trimester, T2- 2nd trimester, T3- 3rd trimester and T4- 3 months postpartum.

Out of 17 pregnancies, 1 patient was in drug free remission throughout the stages. 1 patient had onset in T4 stage. 1 patient had onset of symptoms at 1 month before conception. So total pregnancies at T0 was 14. Six pregnancies had class I MGFA and 8 had class II MGFA at T0.

In T1, total pregnancies were 15 including the patient diagnosed at 1 months before conception. 8 pregnancies had class I MGFA, 6 had class II and 1 had class III MGFA. One patient had a worsening from class II to class III. 2 patients had an improvement from class II to class I MGFA and the remaining pregnancies had no change in clinical status. Hence on comparing T0 and T1, 2 pregnancies had an improvement in MGFA and 1 had a worsening.

In T2, 3 patients had abortions and total pregnancies were 12. Two patients had a worsening from class I MGFA to class II MGFA.Remaining 10 pregnancies had no change. 5 pregnancies were class I and 7 were class II MGFA.The patient who had a worsening from class II to III in T1 had abortion.

In T3, there was no change compared to T2 with 5 subjects with class I and 7 having class II MGFA.

In T4, there were total 16 subjects (excluding the 1 patient in remission and after including 1 patient with onset at 3 months postpartum and 3 abortions), among them 5 were class I, 10 were class II and 1 was having class III MGFA. 1 patient who was MGFA III and had abortion (at T1)

had an improvement in T4. 12 subjects had no clinical change and 3 subjects had a worsening; 2 from class I to class II (including 1 abortion) and 1 from class II to class III.

We analysed overall change in MGFA status by comparing worst MGFA at T0 to T4 and found that one pregnancy had an improvement in clinical status,12 pregnancies had no change and 3 pregnancies had a deterioration of MGFA clinical status.

We analysed overall change in mean MGFA ranks in each stage using Friedman test and p- value was 0.031(<0.05) which was significant. However on analysis of pairwise comparison of MGFA from T0 to T4 using Wilcoxon Signed Rank test, none of the p- values were found to be significant.

Figure 10. The order of pregnancies in the cohort

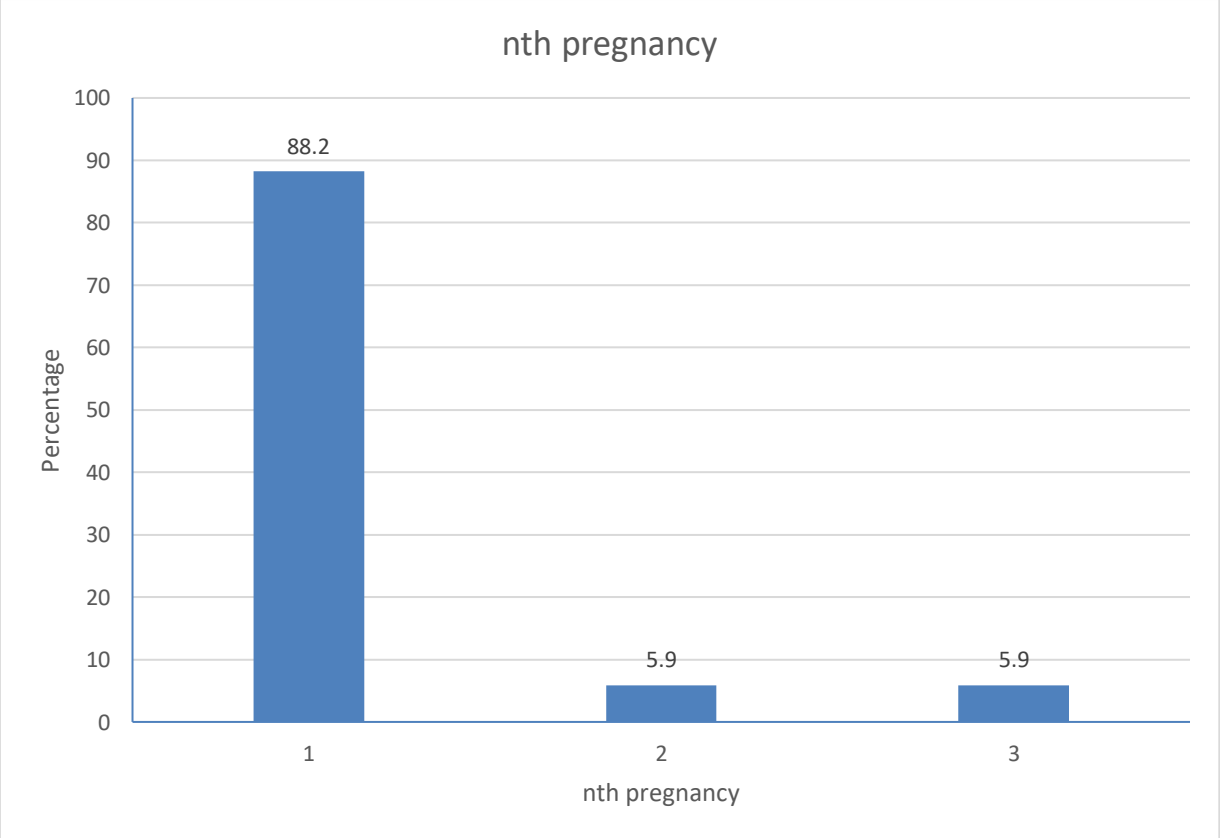
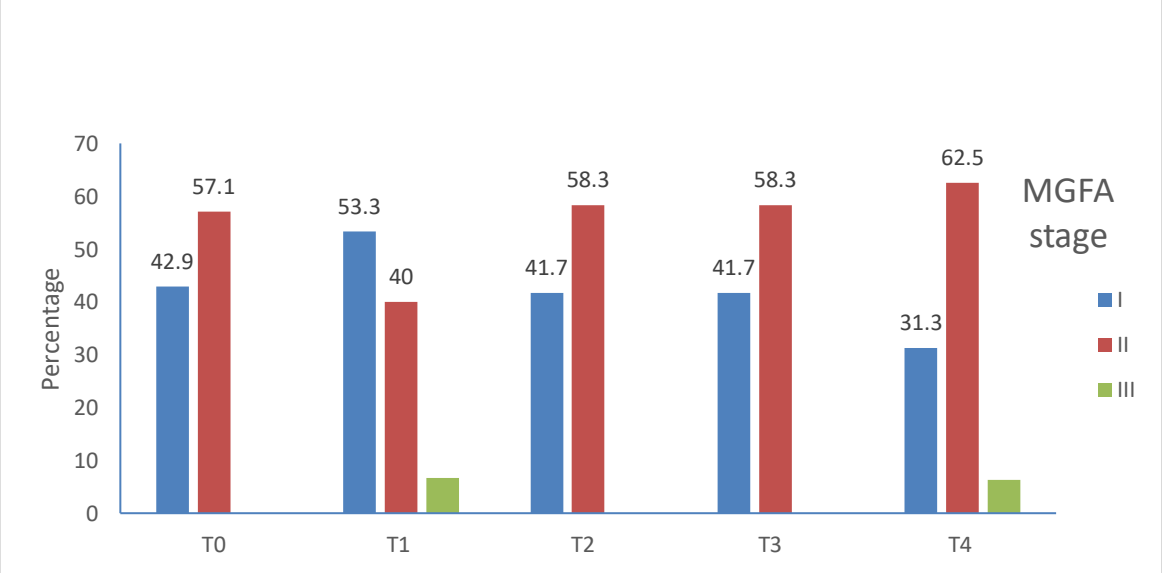


Table 5. Frequency and proportion of MGFA score in various stages

MGFA Stage	T0	T1	T2	T3	T4
	N (%)	N (%)	N (%)	N (%)	N (%)
I	6 (42.9)	8(53.3)	5(41.7)	5 (41.7)	5 (31.3)
II	8(57.1)	6(40)	7(58.3)	7 (58.3)	10 (62.5)
III	0(0)	1(6.7)	0(0)	0 (0)	1 (6.3)
Total	14	15	12	12	16

Figure 11. Distribution of MGFA status during various stages



T0-3 months prepregnancy, T1- 1st trimester, T2- 2nd trimester, T3- 3rd trimester and T4- 3 months postpartum

Figure 12. Scatter diagram showing change in MGFA during various stages

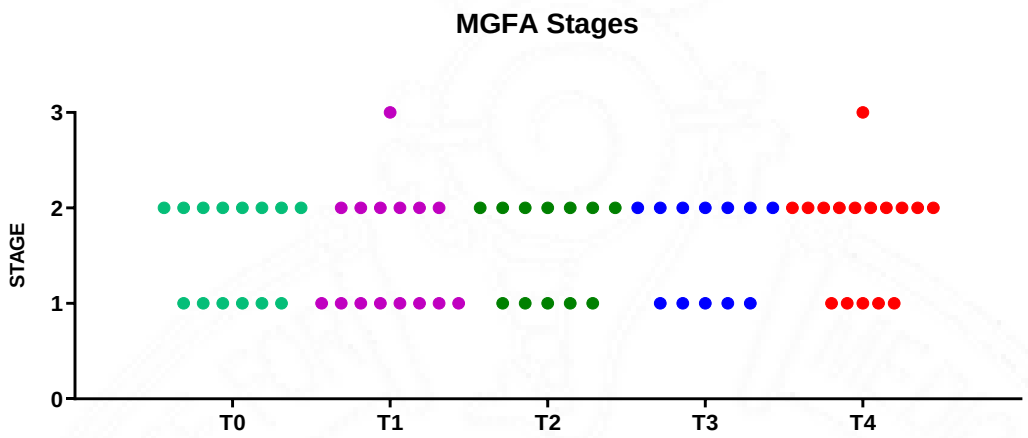


Table 6. Statistical analysis of MGFA distribution using Friedman test

Friedman Test	Mean Rank
MGFA T0	2.95
MGFA T1	2.5
MGFA T2	2.95
MGFA T3	2.95
MGFA T4	3.64

p = 0.031

T0-3 months prepregnancy, T1- 1st trimester, T2- 2nd trimester, T3- 3rd trimester and T4- 3 months postpartum

Table 7. Statistical analysis of MGFA distribution using Wilcoxon Ranks test

Wilcoxon Signed Ranks Test	Pair wise comparison			
	T0 Vs T1	T1 VS T2	T2 VS T3	T3 VS T4
Z	0.577	1.414	0	1.732
p	0.564	0.157	1	0.083

Table 8. Frequency and proportion of patients with clinical change

MGFA Stage	T0 - T1	T1- T2	T2 – T3	T3 – T4	Overall
	N (%)	N (%)	N (%)	N (%)	N (%)
Improvement	2(14.3)	0 (0)	0(0)	1(5.9)	1(6.3)
No change	11(78.6)	10 (83.3)	12(100)	12 (70.6)	12(75)
Deterioration	1(7.14)	2(16.7)	0 (0)	4(23.5)	3(18.8)

T0-3 months prepregnancy, T1- 1st trimester, T2- 2nd trimester, T3- 3rd trimester and T4- 3 months postpartum

Figure 13. Distribution of change in MGFA with comparison to other stages

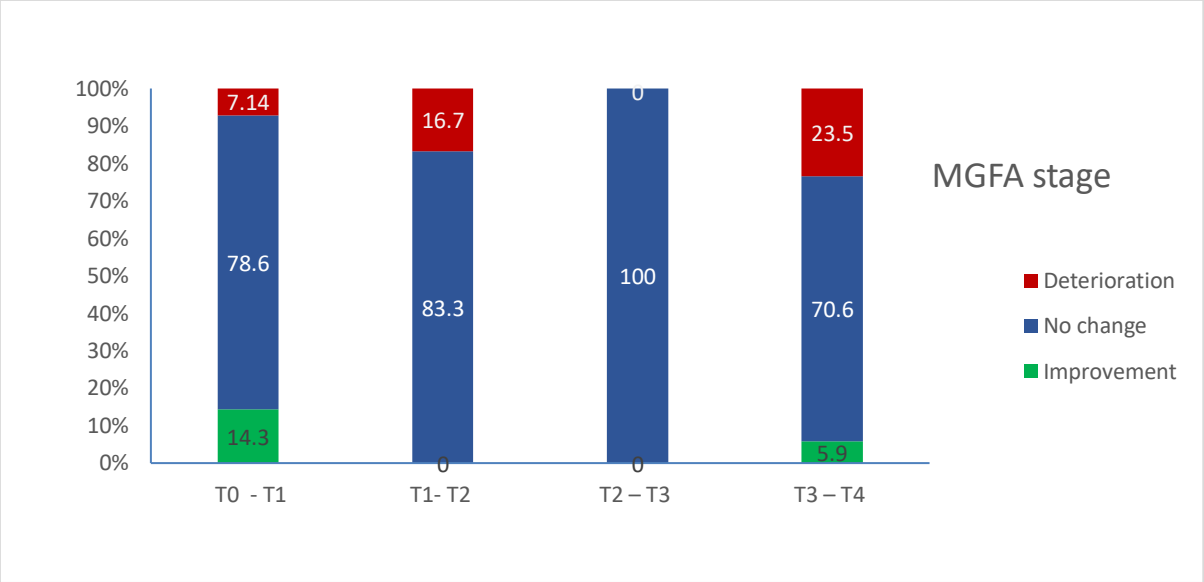


Figure 14. Proportion of overall change in clinical status

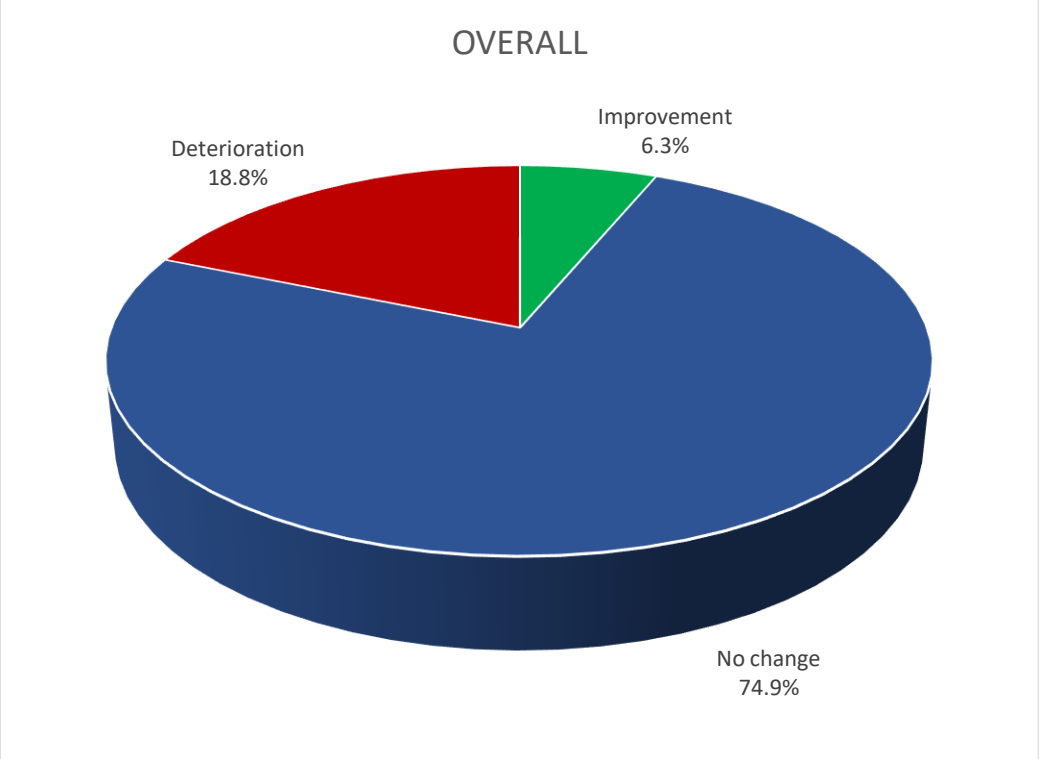


Table 9. Course of myasthenia clinical status during pregnancy

	MGFA AT T0	T1	T2	T3	T4
P1	Onset at post partum	-	-	-	II
P2	II	improvement	No change	No change	Worsening
P3	II	No change	No change	No change	Worsening
P4	II	worsening	Abortion	Abortion	Improvement
P5	I	No change	worsening	No change	No change
P6	II	No change	No change	No change	No change
P7	I	No change	No change	No change	No change
P8	II	improvement	worsening	No change	No change
P8a	II	No change	No change	No change	No change
P8b	II	No change	Abortion	Abortion	No change
P9	I	No change	No change	No change	No change
P10	II	No change	No change	No change	No change
P11	I	No change	No change	No change	No change
P12	Remission	Remission	Remission	Remission	Remission
P13	I	No change	No change	No change	worsening
P14	Onset 1 month prior to preg	II	No change	No change	No change
P15	I	No change	Abortion	Abortion	No change

Six pregnancies were class I MGFA and 8 were class II MGFA at T0. Compared to T0, in T1, two pregnancies had an improvement in MGFA and one had a worsening. In T2, compared to T1, 2 patients had a worsening from class I MGFA to class II. In T2, five pregnancies were class I and seven were class II MGFA. There was no change from T2 to T3. In T4, five were class I, ten were class II and 1 was class III MGFA. One patient who was MGFA III and had abortion

(at T1) had an improvement in T4. Three pregnancies had a worsening in T4; 2 from class I to class II (including 1 abortion) and 1 from class II to class III MGFA.

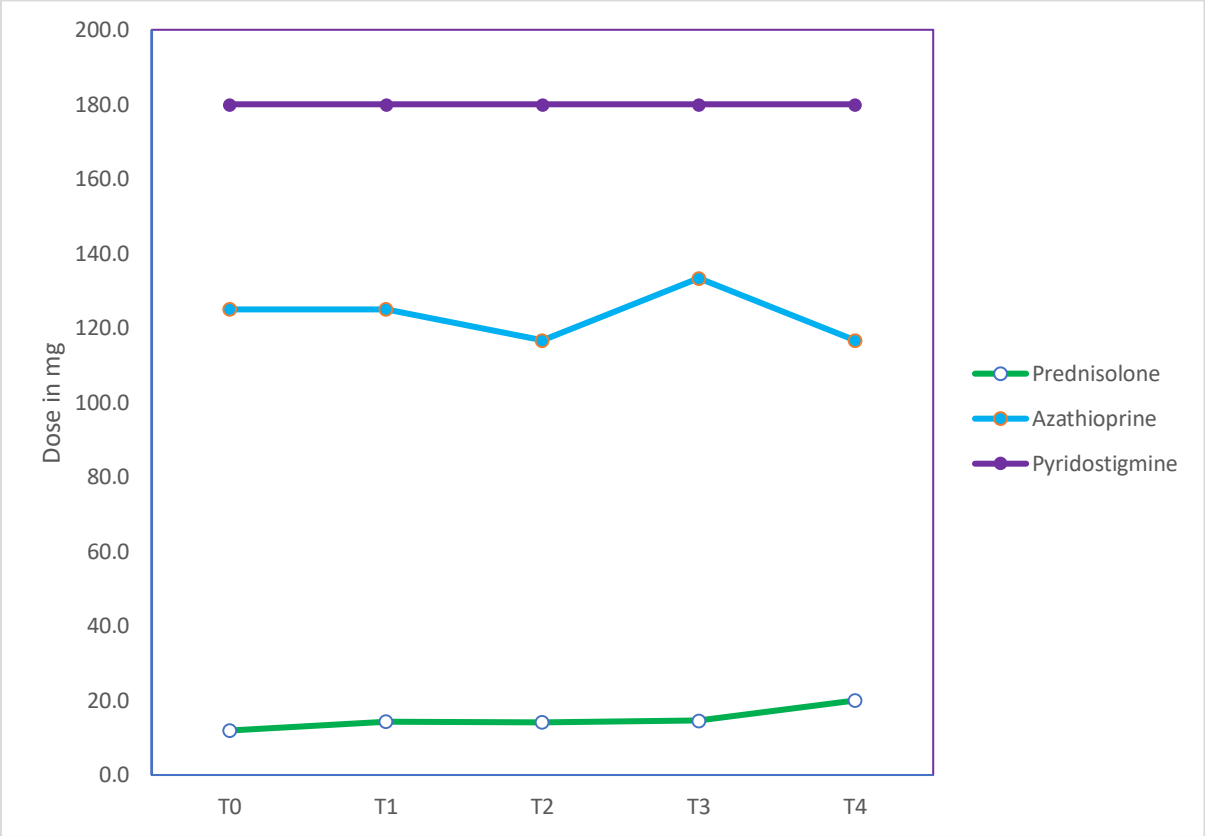
THERAPY BEFORE AND DURING PREGNANCY

Nine subjects were on oral prednisolone (range 5- 20 mg) at T0 and there was no major escalation in dose. At T4, the minimum and maximum doses used were 15 and 40 mg respectively. 4 subjects were on azathioprine at T0, and mean dose was 125 ± 28.9 mg which reduced to 116.7 ± 28.9 in T4. Thirteen subjects were on pyridostigmine at T0 and mean dose used was 180 mg ± 24.5 mg. None of the subjects had major drug related adverse effects. None of our subjects received iv immunoglobulin or therapeutic plasma exchange at any stage.

Table 10. Mean dose (mg) of medications used in various stages

Dose in mg	Prednisolone		Azathioprine		Pyridostigmine	
	Mean ± sd	Range	Mean ± sd	Range	Mean ± sd	Range
T0	11.9 ± 4.3	5-20	125 ± 28.9	100-150	180 ± 24.5	120-240
T1	14.4 ± 4.2	10-20	125 ± 28.9	100-150	180 ± 0	180-180
T2	14.2 ± 3.8	10-20	116.7 ± 28.9	100-150	180 ± 0	180-180
T3	14.6 ± 3.3	10-20	133.3 ± 28.9	100-150	180 ± 0	180-180
T4	20 ± 8.3	15-40	116.7 ± 28.9	100-150	180 ± 23.5	120-240

Figure 15. Mean dose of medications in various stages



PREGNANCY OUTCOMES IN MYASTHENIA PATIENTS

Out of 17 pregnancies, 1 (5.9%) patient had gestational diabetes mellitus and 1(5.9%) had anaemia complication pregnancy. Both the conditions were treated and drug related complications were excluded.

Three subjects had abortions at 2 months of amenorrhoea. One was obstetrician advised medical termination of pregnancy and rest 2 were spontaneous abortions and manifested as bleeding pervaginum.

There were total 3 abortions, 1 preterm delivery and 13 full term deliveries in our group.

Out of 14 deliveries, 8 were spontaneous, 1 was forceps assisted. Among the spontaneous vaginal delivery, 1 patient had preterm labour 3 weeks prior to the date. Among the 6 LSCS, all were term deliveries, 1 had premature rupture of membranes, 1 was post date, 1 had oligohydramnios and reduced fetal movements and remaining were elective as advised by Obstetrician. There were no perinatal complications during labour. There was no incidence of any puerperial infections including endometritis or cystitis. All the 14 mothers were lactating at 3 months postpartum.

Figure 16. Proportion of patients with LSCS

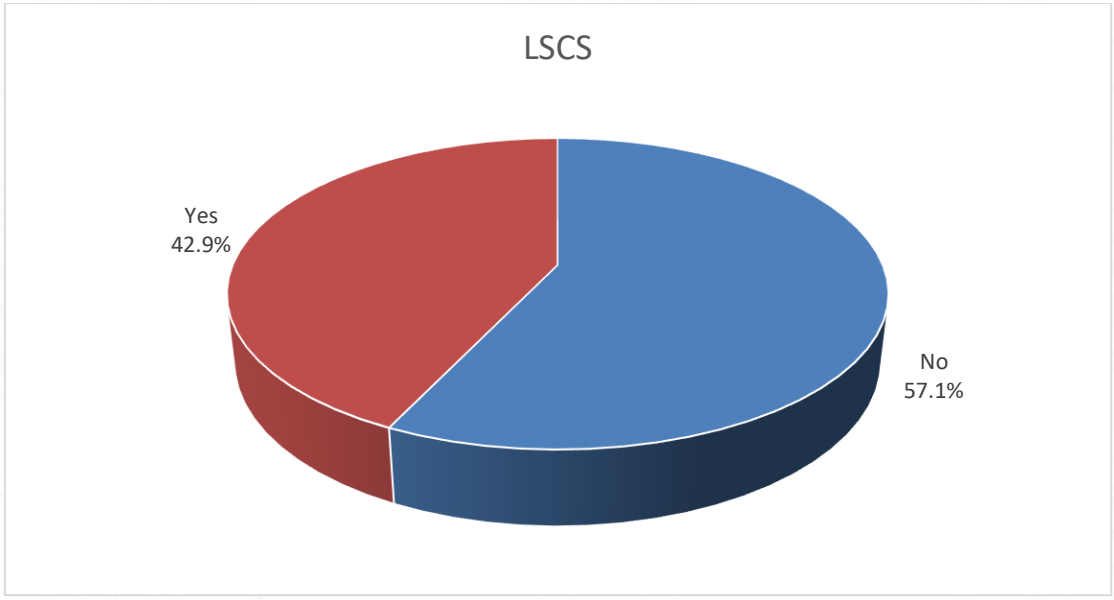
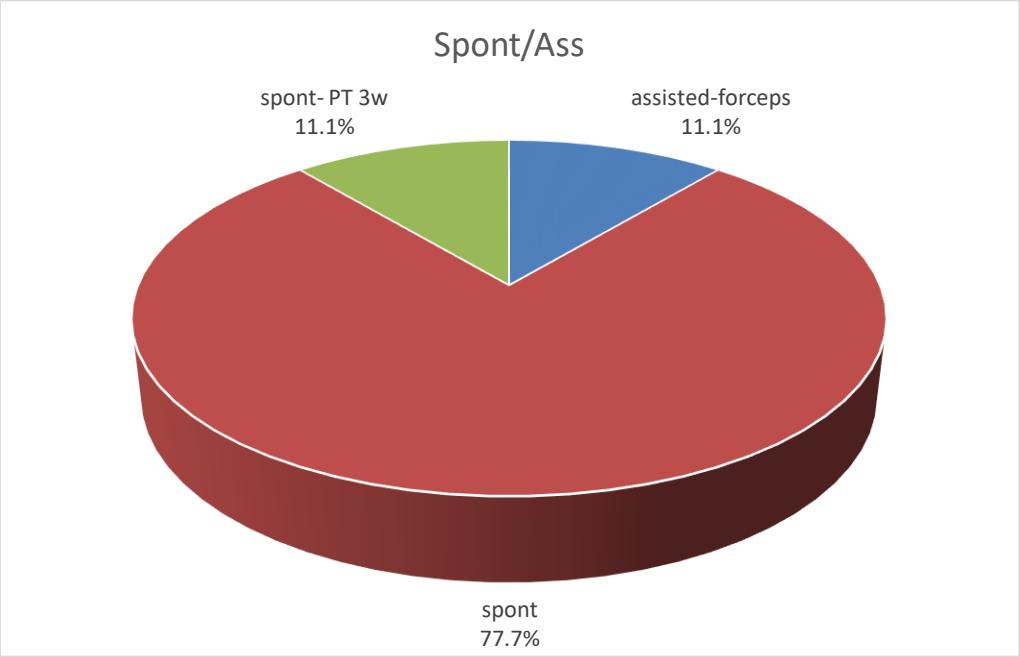


Figure 17. Proportion of patients with spontaneous and assisted deliveries



NEONATAL OUTCOMES

The mean BW was 2.7 ± 0.3 kg with minimum BW of 2.3 kg and maximum BW of 3.2 kg.

Out of 14 babies, 1minute APGAR was 7 in 13/14 and was 5 in 1/14.Similarly 5 minutes APGAR was 8 in 12/14 babies and 6 in 2/14 babies. No neonate had any congenital anomalies.

APGAR stands for Appearance, Pulse, Grimace, Activity, and Respiration. APGAR score of 7,8,9 is considered normal

Among the 14 neonates, 2 had poor feeding, feeble cry and mild hypotonia and presumed to be having TNMG. Babies were observed and were given breast feeding and had spontaneous improvement in 3-4 days. There was no need for Non invasive ventilation or mechanical ventilation in those 2 neonates.

Figure 18. Boxplot showing the mean birthweight

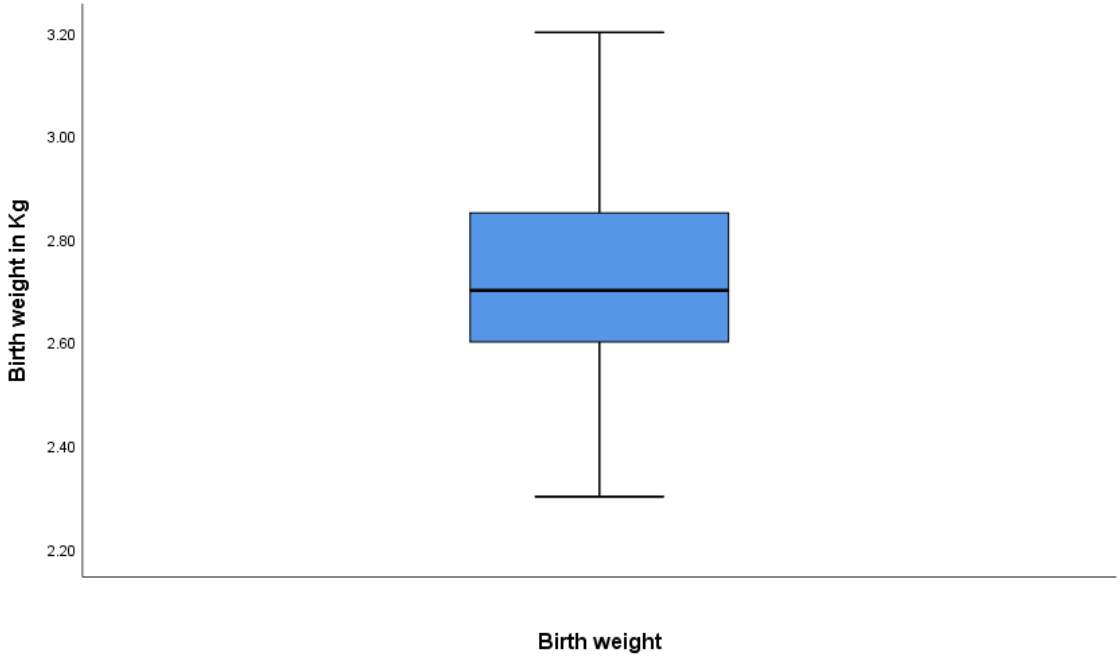


Figure 19. Proportion of neonates with poor APGAR score

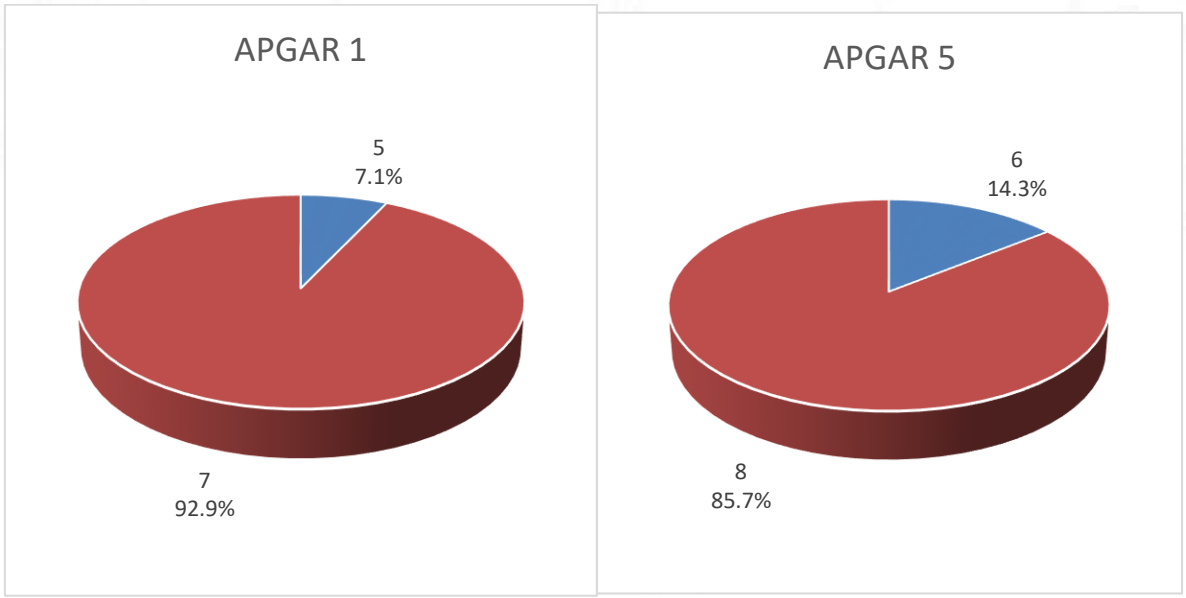


Figure 20. Proportion of transient neonatal myasthenia gravis

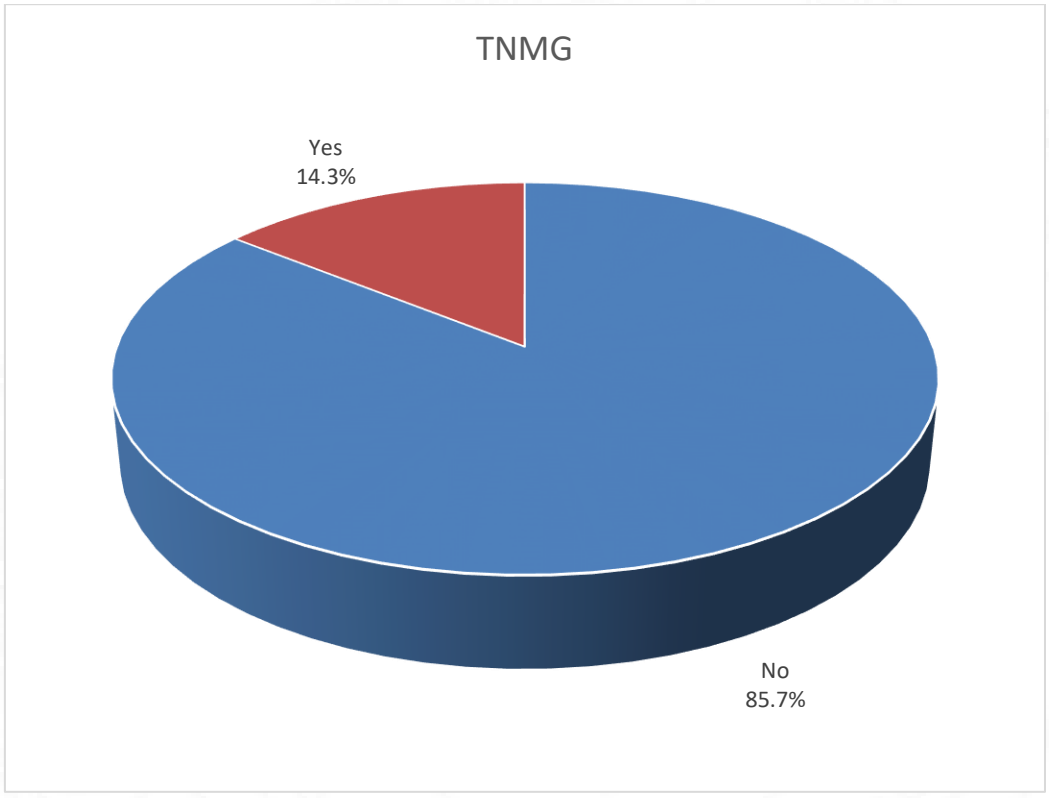


Table 11. Pregnancy and neonatal outcome for all patients

	PREGNANCY OUTCOME				NEONATAL OUTCOME		
	Medical complications	Delivery LSCS/Spontaneous	Preg complication	Preterm/Term	Birth weight (kg)	APGAR 1minute/5minute	TNMG
P1	nil	LSCS	Post date	Term	3.2	7/8	No
P2	Nil	LSCS	Reduced fetal movements	Term	2.7	7/8	No
P3	Nil	Spontaneous	Nil	Term	2.8	7/8	No
P4	Nil	-	abortion	-	-	-	-
P5	Nil	Spontaneous Assisted forceps	Nil	Term	2.7	5/6	Yes
P6	Nil	Spontaneous	Nil	Term	2.4	7/8	No
P7	Nil	Spontaneous	Nil	Term	2.7	7/8	No
P8	Nil	LSCS	Oligohydramnios	Term	2.85	7/8	No
P8a	Anaemia	LSCS	Nil	Term	2.3	7/8	No
P8b	Nil	-	Abortion	-	-	-	-
P9	Nil	Spontaneous	Nil	Term	2.6	7/8	No
P10	Nil	LSCS	PROM	Term	2.7	7/6	Yes
P11	Nil	Spontaneous	Nil	Term	3	7/8	No
P12	Gestational Diabetes	Spontaneous	Nil	Preterm-3 weeks	3.2	7/8	No
P13	Nil	LSCS	Nil	Term	2.75	7/8	No
P14	Nil	Spontaneous	Nil	Term	2.5	7/8	No
P15	Nil	-	Abortion	-	-	-	-

DISCUSSION

Literature pertaining to myasthinia gravis and pregnancy are limited especially from India. Generally pregnancy is associated with a physiological immunosuppression accounting for an increased incidence of infections and improvement in some autoimmune diseases (53). Conversely this may not be very true for diseases like systemic lupus erythematosis and myasthenia gravis where a worsening of symptoms during pregnancy is also frequently reported. Previous studies suggested that clinical course of MG is highly variable in pregnancy. In this study, we reveiwed 17 pregnancies in 15 myasthenia patients.

Many previous studies showed that about one third of myasthenic patients have exacerbations during pregnancy, another one third have no change and remaining may have an improvement. Schlezinger et al., reported this first in 1955 in their study, where exacerbations occured predominantly in the first trimester (54). Another study of 69 pregnancies by Djelmis et al., reported a similar finding, however the exacerbations predominantly occurred in the later trimesters of pregnancy (36). Mitchel et al., in 1992 reported majority had a worsening in third trimester in a study of 11 patients (55). Another study of 13 patients reported worsening in 42 % cases (56). Batochi et al., showed 42% had no change, 39% had improvement and 19% deteriorated with worsening occuring more frequently in the second trimester (42).

All these previous studies suggest a highly variable and unpredictable course of MG in pregnancy. Our study showed deterioration has occurred for 18.8% of all pregnancies including new onset of symptoms in one patient in the postpartum period. Deterioration occured predominantly in the post partum period although worsening happened for one patient in the 1st trimester. Immediate worsening in the postpartum period could be due to bodys immunologic restoration following delivery or precipitated by puerperial infections like endometritis or cystitis however there was no evidence for infections in our patients. We found overall progression of MGFA status across various stages significant with a p- value of 0.031 ($p < 0.05$) when analysed with nonparametric Friedmans test however the results were not consistent with further pair wise

analysis. 75 % pregnancies showed no change, 6.1% had an improvement and no pregnancy produced a clinical remission. One patient who was already in remission at the time of conception did not get any change during pregnancy or postpartum.

In our group, all patients were optimised on medications in the prepregnacy stage and this could have resulted in a better control as suggested by absence of exacerbations at any stage. A similar study in 2004 also reported similar finding of no exacerbations (57). One patient in our study had 2 livebirths and 1 abortion; her clinical course remained stable in all pregnancies while continuing on medications. Batochi et al., suggested that clinical course during one pregnancy may not predict the course in subsequent pregnancies (42).

In our study, analysis of a stage wise worsening across pregnancy using MGFA scores was done and we estimated an overall worsening from prepregnancy to postpartum state also.The findings again indicate that clinical course of MG during pregnancy may have many twists and turns and ensurance of a proper treatment and control of symptoms in the prepregnancy state would contribute to a relatively uneventful pregnancy.However this possibility needs propsective studies for further validation.

Previous studies reported that the highest risk of mortality is in the first year after onset of disease and there is only minimal risk 7 years after the onset of the disease. There was no mortality in our group.

Table 12. Frequency of worsening and stage of deterioration in previous studies

Study	Number of subjects	Frequency of clinical change	Stage of deterioration
Schlezinger et al. (54)	22 women and 33 pregnancies	Exacerbation in 1/3rd, Remission or no change in 2/3rd	Exacerbation in 1st trimester
Djelmis et al.(36)	69 pregnancies in 65 women over a 28 year period	Exacerbation in 1/3rd, no change in rest of pregnancies	Exacerbation predominantly in postpartum and puerperium
Mitchel et al. (55)	11 pregnancies	Worsening in 2/3rd and improvement in 1/3rd	Exacerbation mainly in 3rd trimester
Batochi et al.(42)	47 preganant women	Worsening in 19%, no change 42 %, improvement in 39%	Maximum exacerbation in 2nd trimester
Zenteno et al.(58)	18 pregnant women	Worsening in 33%	Maximum worsening in 2nd trimester
Picone et al.	12 pregnant women	Worsening in 42%	

Three pregnancies had abortions in our study; 2 spontaneous and 1 induced probably due to the disease. All abortions occurred in the second month of pregnancy. Out of the total 3 abortions, two pregnancies had MGFA score of II at 3 months before conception and one had MGFA I. A patient who had an abortion had a worsening of MGFA from II to III in the first trimester. A review by Plauche et al., reported 113 MG patients and 164 pregnancies with 35.4% showing exacerbations. They reported 28 abortions- 14 spontaneous and 14 induced along with

6 maternal deaths and 12 perinatal deaths (59). Djelmis et al., reports 11 induced abortions which were unrelated to their primary disease (36).

Myasthenia gravis has an overlap with other autoimmune diseases, the most common being Hashimotos thyroiditis. In our study, 1 patient had gestational diabetes mellitus which resolved after delivery.

Regarding labour, 42.9% delivered through Caesarian section in this study. Indications were oligohydramnios, post date and reduced fetal movements. One had forceps assisted spontaneous delivery. Study by Jose et al., reported similar results to our study ie. 47 % deliveries by Caesarian section and remaining vaginally with 1 forceps assisted delivery (58). Djelmis et al., reported 82% vaginal deliveries, Batochi et al., reported 70%, Picone et al., in 58 % and Mitchel et al., in 90%. A retrospective comparison study by Hoff et al., had 127 pregnancies compared with 1.9 million deliveries by normal mothers showed that pregnant myasthenics have a 3 times higher risk for preterm rupture of membranes compared to normal group.Rate of Caesarian section was doubled in the study group and they had concluded an increased risk of complications during labour (38). Caesarian section may cause a sudden worsening of myasthenia in the immediate post partum with additional concern regarding use nondepolarising muscle blockers for anaesthesia also. A vaginal delivery is preferred and should be adequately supported by pharmacological armamentorium.

Regarding treatment, most patients were on oral prednisolone, azathioprine, neostigmine and pyridostigmine. No patient was given iv immunoglobulins or underwent plasma exchange.
All pregnancies were well controlled by medications in the prepregnancy stage and there was no major dose escalations. There was modification of drugs in response to MGFA worsening. One patient in our cohort had PROM, could be due to concomitant steroid use which was reported previously. No cleft lip was reported associated with steroid use.

Some of the adverse effects in the children of mothers treated with azathioprine were teratogenicity, chromosomal effects,immunologic and hematologic depression, low birth weight, and abortion (60). Our group had 3 abortions and 1 patient who had a spontaneous abortion was on azathioprine. There was no major congenital malformation or birth defects reported.

Four patients in our cohort underwent thymectomy before pregnancy and 1 had undergone the procedure after pregnancy.There are case reports where thymectomy produces rapid improvement in myasthenic symptoms in pregnancy (61). In a study by Roth et al., clinical course of symptoms seems to be unpredictable during both, pregnancy and postpartum period in both thymectomised and nonthymectomised groups (62). But they suggested that thymectomised women getting conceived may handle myasthenic crisis better than nonthymectomised ladies. This observation goes in concordance with our study also; all patients with thymic pathology underwent thymectomy and none of our patients had myasthenic crises.

There was only 1 preterm delivery in our group, and it was a spontaneous vaginal delivery. Premature rupture of membrane was present in 1 pregnancy who got delivered by Caesarian section but it was a term delivery. Hoff et al., study suggested PROM was thrice common in myasthenia group than the reference group (38). In a recent study by Tanacan et al., pregnancies with worsening were more likely to have higher abortions, preterm labour, preterm premature rupture of membranes, LSCS, and TNMG (63).

The minimum birth weight in our group was 2.3 kg. There was no significantly low birth weight reported in our group especially considering the medication status of our patients. Neonatal status was assessed with APGAR score. One baby had 1minute APGAR of 5 and 2 babies had 5 minute APGAR of 6. 2 babies in our group had hypotonia, poor feeding and feeble cry for 3-4 days after delivery, and spontaneously improved after careful observation and breast feeding. The clinical symptomatology is suggestive of transient neonatal MG eventhough antibody titres were not measured in these neonates. These clinical features were most consistent with the phenotype

of typical TNMG previously reported in literature. No baby had Arthrogryposis which is a severe form of TNMG. Incidence of TNMG in our study was 14.3%. None of the babies in our group required mechanical ventilation. TNMG was present in 1 baby of mother who had MGFA deterioration. Previous studies reported an incidence of TNMG between 10 to 30 % and complete recovery within 1 month is the norm (58). The incidence was even lower, about 5% in another study (58).

Two AchR antibody negative patients in our group were later found to be MuSK antibody positive. However there was no major exacerbation in those patients during any stage of pregnancy. There is a paucity of data describing the course of pregnancy in MuSK myasthenia. Previous studies suggest milder symptoms during pregnancy and presence of TNMG in neonates of MuSK antibody positive mothers (64) (65). However we postulate that proper control of myasthenic symptoms and early thymectomy in the prepregnancy stage itself could be a factor in avoiding exacerbations during pregnancy.

MERITS AND LIMITATIONS

Our study is the first of its kind from India where no previous studies were reported analysing course and outcome of myasthenia in pregnancy except few case reports. We have categorised patients based on MGFA score into no change, remission, deterioration and improvement and analysed stage wise change in MGFA prepregnancy to postpartum periods. This study provides insight into the variable nature of clinical course of Myasthenia in pregnancy eventhough overall none of our patients had a life threatening exacerbation or requirement of IvIg or PLEX. The reason for this being whether our subjects on adequate pharmacotherapy or due to the unpredictability of disease course itself needs to be ascertained through further studies. We have also made a note on MuSK antibody positive patients and pregnancy about which the

literature is scarce. We also addressed pregnancy and neonatal outcome in the presence of myasthenia along with pregnancy effect on myasthenia.

Our study has the following demerits also; it is a retrospective chart based review and sample size was small. No comparisons were made with a control group such that complications occurred during pregnancy like abortions and PROM and neonatal outcomes of transient myasthenia are significant or not could not be ascertained. Two babies had presumed TNMG but antibody titres were not measured and a correlation between maternal antibody titre and severity of TNMG was also not assessed in our study.

CONCLUSIONS

- Out of 227 females with myasthenia gravis, 15 subjects satisfied the inclusion criteria and a total of 17 informative pregnancies were analysed.
- Around one third of subjects had only ocular MG at onset and 53 % were AchR antibody and 2% were MuSK antibody positive.
- In the prepregnancy stage, all the subjects had mild weakness either having class I or class II MGFA score.
- Myasthenia gravis course during pregnancy was generally unchanged with a deterioration of clinical status predominantly in the postpartum period (in 4 pregnancies) followed by a worsening in 2 pregnancies in 2^{nd} trimester and 1 pregnancy in 1^{st} trimester.
- Regarding pregnancy outcome, 3 pregnancies had abortions; 2 spontaneous and 1 induced abortion and 2 subjects with spontaneous abortions were on immunomodulation with steroids and azathioprine and all 3 patients with abortions were on cholinesterase inhibitors.
- About 86% of subjects were on pyridostigmine, 52% were on oral steroids and 26% on azathioprine during first trimester of pregnancy and 43% were on all the three medications together.
- 42.9 % pregnancies were delivered by Caesarian section and among the eight spontaneous deliveries, one was assisted delivery and one was preterm delivery.
- Fetal outcome analysis showed poor APGAR scores in two neonates and presumed typical TNMG in 2 babies and there were no congenital anomalies.

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APPENDIX

ABBREVIATIONS

MG – Myasthenia gravis

NMJ – Neuromuscular junction

AchR – Acetyl choline receptor

MuSK – Muscle specific kinase

LRP-4 – Lipoprotein related protein-4

WHO – World Health Organisation

LEMS – Lambert Eaton Myasthenic syndrome

MGFA – Myasthenia gravis Foundation of America

RNS – Repetitive nerve stimulation

SFEMG – Single fibre electromyography

TNMG – Transient neonatal myasthenia gravis

NMG - Neonatal myasthenia gravis

IUD – Intrauterine death

BW – Birth weight

LSCS – Lower segment Caesarian section

APGAR – Appearance, Pulse, Grimace, Activity, and Respiration

PROM – Premature rupture of membranes

PLEX – Plasma exchange

PATIENT INFORMATION SHEET

TITLE OF THE STUDY: 'A retrospective study on Pregnancy in Myasthenia gravis'

Investigators:

1. Principal Investigator: Dr Harikrishnan R, Neurology resident, Department of Neurology
2. Co- investigator: Dr M D Nair, Professor and Head, Department of Neurology
3. Co- Investigator: Dr Sruthi S Nair, Assistant Professor, Department of Neurology

Sir/ madam,

We invite you to take part in our study titled 'A retrospective study on pregnancy in Myasthenia gravis'**.** Before you agree to participate in this research study, it is important that you read and understand this information sheet which will provide you with all the information needed for participation in this study so that you can make a well informed and considered decision about participation. In addition, should you have any questions, the investigator and her team members will be happy to answer them and explain to you more about this research study, the procedure involved and the related issues. You may ask them any questions you may have regarding the study, or ask them to explain any word or information that you don't clearly understand.

You are being asked to participate in this study as you have been diagnosed with a neurological disease called Myasthenia gravis. 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.

What is the purpose of this study?

- The purpose of this study is to learn the effect of pregnancy on the course of myasthenia gravis, MG on pregnancy outcome and influence of drugs for MG on pregnancy outcome.

If you take part what will you have to do?

If you agree to participate in this study, you will be required to undergo an interview and physical examination and examination of your old documents by the examiner. During the study, you might give the data regarding your disease exacerbations and remissions during your pregnancy,any other comorbidities during your pregnancy,fetal outcome, any neonatal problems and the medications which you were taking before and after the pregnancy.

Your participation in the study is purely voluntary, you have right to deny participation or withdraw consent, and there will be no difference in your treatment or follow up if you decide not to cooperate for the study.

Will you have to pay for the investigations?

You will not be charged for clinical examination.

Any other treatment or investigation that is required for you will continue as previously and the usual arrangements that you have with the hospital will decide how much you pay for this.

What happens if you are detected to have any fresh problems during the study?

If our studies detect any new problem for you, we will direct you to your treating doctor for the appropriate management after discussing with you.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask Dr.Harikrishnan R **(Tel: 8078135023)** or email: hkrmnr@sctimst.ac.in

Name of the PI: Dr Harikrishnan R

Address and Contact Details: Senior Resident, Department of Neurology, SreeChitraTirunal Institute for Medcial Sciences and Technology, Medical College PO, Trivandrum -11

Tel :8078135023

Signature of the PI:

For any clarifications regarding the study's ethics clearance you may contact the Member Secretary of the SCTIMST-IEC. The phone number is: 0471-2524234, and the email id isiec.mem.sec@sctimst.ac.in

INFORMATION SHEET IN MALAYALAM

കാര്യവിവരണപത്രം

പഠന ശീർഷകം

മയസ്തീനിയ ഗ്രാവിസ് ഉള്ളവരിലെ ഗർഭാവസ്ഥയെപ്പറ്റിയുള്ള ഒരു ഭൂതകാലാധിഷ്ഠിത പഠനം

ഗവേഷകർ:

1. മുഖ്യ ഗവേഷകൻ.: ഡോ. ഹരികൃഷ്ണൻ ആർ, ന്യൂറോളജി റെസിഡന്റ്, ഡിപ്പാർട്ട്മെന്റ് ഓഫ് ന്യൂറോളജി
2. സഹ ഗവേഷകൻ: ഡോ എം. ഡി. നായർ, പ്രൊഫസർ, ഡിപ്പാർട്ട്മെന്റ് ഓഫ് ന്യൂറോളജി
3. സഹ ഗവേഷക: ഡോ ശ്രുതി നായർ, അസിസ്റ്റന്റ് പ്രൊഫസർ, ഡിപ്പാർട്ട്മെന്റ് ഓഫ് ന്യൂറോളജി

ശ്രീ/ശ്രീമതി,

താങ്കളെ ഞങ്ങളുടെ 'മയസ്തീനിയ ഗ്രാവിസ് ഉള്ളവരിലെ ഗർഭാവസ്ഥയെപ്പറ്റിയുള്ള ഒരു ഭൂത കാലാധിഷ്ഠിത പഠനം' എന്ന ഗവേഷണത്തിൽ പങ്കെടുക്കുവാൻ ക്ഷണിക്കുന്നു.

ഈ ഗവേഷണ പഠനത്തിൽ പങ്കെടുക്കാൻ താങ്കൾ തീരുമാനിക്കുന്നതിനു മുൻപ് പഠനത്തിൽ പങ്കെടുക്കാനാവശ്യമായ വിവരങ്ങൾ നൽകുന്ന ഈ കാര്യവിവരണപത്രം ശ്രദ്ധയോടെ വായിക്കുക എന്നത് പ്രധാനമാണ്. അത് കാര്യവിവരത്തോടെയും വേണ്ടുന്ന പരിഗണനകളോടെയും പങ്കാളിത്തത്തെപ്പറ്റി തീരുമാനമെടുക്കുന്നതിന് സഹായിക്കും. കൂടാതെ താങ്കൾക്കെന്തെങ്കിലും ചോദ്യങ്ങളുണ്ടെങ്കിൽ ഗവേഷകനും സംഘാംഗങ്ങളും ഈ പഠനത്തെപ്പറ്റിയും, നടപടികളെപ്പറ്റിയും ബന്ധപ്പെട്ട പ്രശ്നങ്ങളെപ്പറ്റിയും വിശദമായ മറുപടി നൽകാൻ സന്തോഷമുള്ളവരാണ്. പഠനവുമായി ബന്ധപ്പെട്ട് താങ്കൾക്കു ഏതുചോദ്യമോ അല്ലെങ്കിൽ വ്യക്തമായി മനസ്സിലാകാത്ത എത് വാക്കിനെപ്പറ്റിയോ വിവരത്തെപ്പറ്റിയോ ഉള്ള വിശദീകരണം താങ്കൾക്ക് ചോദിക്കാം.

മയസ്തീനിയ ഗ്രാവിസ് എന്നറിയപ്പെടുന്ന ഒരു ന്യൂറജ്ജിക്കൽ രോഗം താങ്കൾക്കുണ്ടെന്ന് കണ്ടെത്തിയതിനലാണ് താങ്കളോട് ഈ പഠനത്തിൽ പങ്കെടുക്കാൻ ആവശ്യപ്പെടുന്നത്. ആർജ്ജിതമായ മയസ്തീനിയ ഗ്രാവിസ് (എംജി) ഒരു ഓട്ടോ ഇമ്മ്യൂൺ രോഗമാണ്, അതിൽ ന്യൂറോ പേശീ സന്ധികളിലെ അസെറ്റിൽകൊളിൻ റിസപ്റ്ററുകൾക്ക് (AChR Abs) എതിരെ ഓട്ടോ ആന്റിബോഡികൾ ന്യറോ പേശീ വിനിമയത്തിൽ തകരാറുണ്ടാക്കുകയും എല്ലുകളുമായി ബന്ധപ്പെടുന്ന പേശികളിൽ ബലഹീനതയ്ക്ക് കാരണമാകുകയും ചെയ്യും.

ഈ പഠനത്തിന്റെ ഉദ്ദേശമെന്താണ്?

ഗർഭാവസ്ഥയുടെ മയസ്തീനിയ ഗ്രാവിസിലെ പ്രഭാവം, ഗർഭത്തിന്റ പരിണിതഫലം, മയസ്തീനിയ ഗ്രാവിസിനുള്ള മരുന്നുകളുടെ ഗർഭാവസ്ഥയിലെ സ്വാധീനം എന്നിവ വിലയിരുത്താനാണ് ഈ പഠനം ഉദ്ദേശിക്കുന്നത്.

താങ്കൾ പങ്കെടുക്കുകയാണെങ്കിൽ എന്തു ചെയ്യണം?

താങ്കൾ പങ്കെടുക്കുവാൻ തീരുമാനിക്കുകയാണെങ്കിൽ ഡോക്ടറുമായുള്ള ഒരു അഭിമുഖത്തിനും ശാരീരിക പരിശോധനയ്ക്കും താങ്കളുടെ പഴയ ചികിത്സാരേഖകളുടെ പരിശോധനയ്ക്കും വിധേയമാകണം. പഠനസമയത്ത്, ഗർഭാവസ്ഥയിൽ താങ്കളുടെ രോഗത്തിന്റെ വർദ്ധനവും ആവർത്തനവും സംബന്ധിച്ച വിവരങ്ങൾ, ഗർഭകാലത്തെ മറ്റ് അനുബന്ധ അസുഖങ്ങൾ, ഭ്രൂണത്തിന്റെ അവസ്ഥ, പ്രസവാനന്തര പ്രശ്നങ്ങൾ, ഗർഭാവസ്ഥയ്ക്കുമുൻപും ശേഷവും കഴിച്ച മരുന്നുകൾ എന്നിവയുടെ വിവരങ്ങളും നൽകേണ്ടിവരും.

ഈ പഠനത്തിലുള്ള താങ്കളുടെ പങ്കാളിത്തം തികച്ചും സ്വമേധയായാണ്, താങ്കൾക്ക് പങ്കെടുക്കാതിരിക്കാനും സമ്മതം പിൻവലിക്കാനും അവകാശമുണ്ട്, പഠനത്തിൽ പങ്കെടുക്കേണ്ടെന്ന് താങ്കൾ തീരുമാനിച്ചാലും താങ്കളുടെ ചികിത്സയിലോ തുടർചികിത്സയിലോ ഒരു മാറ്റവും ഉണ്ടാകില്ല.

പരിശോധനകൾക്ക് താങ്കൾ പണം നൽകണോ?
പരിശോധനകൾക്ക് താങ്കൾ പണം നൽകേണ്ടതില്ല,

താങ്കൾക്കാവശ്യമുള്ള മറ്റ് ചികിത്സകൾ, പരിശോധനകൾ എന്നിവ മുന്നേപ്പോലെ തുടരും. ആയതിന് താങ്കൾ ആശുപത്രിയുമായുണ്ടാക്കിയ ധാരണപ്രകാരം പണം നൽകേണ്ടിവരും.

പഠനത്തിനിടയിൽ താങ്കൾക്ക് പുതുതായി എന്തെങ്കിലും പ്രശ്നമുണ്ടെന്ന് കണ്ടെത്തിയാൽ എന്തു ചെയ്യും?
ഞങ്ങളുടെ പഠനത്തിനിടയിൽ എന്തെങ്കിലും പ്രശ്നങ്ങൾ കണ്ടെത്തുകയാണെങ്കിൽ താങ്കളുമായി ചർച്ച ചെയ്തശേഷം താങ്കളെ ചികിത്സിക്കുന്ന ഡോക്ടറെ കണ്ട് വേണ്ടുന്നതു ചെയ്യാൻ നിർദ്ദേശിക്കും.

എന്റെ വ്യക്തിഗതവിവരങ്ങൾ രഹസ്യമായിരിക്കുമോ?
പഠനത്തിന്റെ ഫലങ്ങൾ ഒരു വൈദ്യശാസ്ത്ര ജർണ്ണലിൽ പ്രസിദ്ധീകരിക്കുമെങ്കിലും താങ്കളെ പേരുകൊണ്ട് പ്രസിദ്ധീകരണത്തലോ പഠനഫലങ്ങളുടെ പ്രദർശനത്തിലോ തിരിച്ചറിയാനാവില്ല. എന്നിരുന്നാലും പഠനത്തിൽ പങ്കെടുക്കുകയാണെങ്കിൽ, താങ്കളുടെ ആരോഗ്യ രേഖകൾ പഠനവുമായി ബന്ധപ്പെട്ട ആളുകൾ താങ്കളുടെ അധികമായ സമ്മതമില്ലാതെ പരിശോധിച്ചേക്കാം.
താങ്കൾക്ക് കൂടുതൽ ചോദ്യങ്ങളുണ്ടെങ്കിൽ ദയവായി ബന്ധപ്പെടുക, (ഫോൺ . **8078135023**)
ഇമെയിൽ. hkrmnr@sctimst.ac.in

മുഖ്യ ഗവേഷകന്റെ പേര്

ഡോ ഹരികൃഷ്ണൻ ആർ

മേൽവിലാസവും ബന്ധപ്പെടാനുള്ള വിശദാംശങ്ങളും

സീനിയർ റെസിഡന്റ്, ന്യൂറോളജി ഡിപ്പാർട്ട്മെന്റ്, ശ്രീചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി, മെഡിക്കൽ കോളേജ് പി. ഒ, തിരുവനന്തപുരം 695011

ഫോൺ. **8078135023**

മുഖ്യ ഗവേഷകന്റെ ഒപ്പ്

പഠനത്തിന്റെ നൈതീക അനുവാദവുമായി ബന്ധപ്പെട്ട വിശദീകരണങ്ങൾക്ക് താങ്കൾക്ക് ബന്ധപ്പെടാം
മെമ്പർസെക്രട്ടറി **SCTIMST- IEC** ഫോൺ . **0471-2524234**
ഇമെയിൽ **isiec.mem.sec@sctimst.ac.in**

MALAYALAM CONSENT FORM

സമ്മത പത്രം

പങ്കെടുക്കുന്ന ആളുടെ പേര് : ജനന തീയതി/വയസ്സ് :

.....മകനായ/മകളായ ഞാൻ..... അടിയിൽ വിവരിച്ചിരിക്കുന്ന കാര്യങ്ങൾ അറിഞ്ഞ് ബോധ്യപ്പെട്ടിരിക്കുന്നു.

(ബോക്സിനുള്ളിൽ (□□) അടയാളപ്പെടുത്തുക).

- മുകളിൽ പറഞ്ഞിരിക്കുന്ന **മയസ്തീനിയ ഗ്രാവിസ് ഉള്ളവരിലെ ഗർഭാവസ്ഥയെപ്പറ്റിയുള്ള ഒരു ഭൂതകാലാധിഷ്ഠിത പഠനം** എന്ന പഠനത്തെ കുറിച്ചുള്ള വിവരങ്ങൾ ഞാൻ വായിച്ചു മനസ്സിലാക്കി.
  എനിക്ക് ഉണ്ടായിരുന്ന സംശയങ്ങൾ ഞാൻ ചോദിച്ച് മനസ്സിലാക്കിയിട്ടുണ്ട്. [ ]
- ഈ പഠനത്തിൽ പങ്കെടുക്കുന്നതിന് എന്റെ മാത്രം തീരുമാനമാണെന്നും എനിക്ക് എപ്പോൾ വേണമെങ്കിലും ഇതിൽ നിന്നും പിൻമാറാം എന്നും ഞാൻ മനസ്സിലാക്കുന്നു. അത് എന്റെ ചികിത്സയെയോ എന്റെ അവകാശങ്ങളേയോ ബാധിക്കുകയില്ലയെന്നും ഞാൻ മനസ്സിലാക്കുന്നു. [ ]
- അധികമായ വൈദ്യ പരിശോധകളും പഠനത്തിനായുള്ള സൗജന്യമാണെന്നും പതിവ് പരിശോധനകളുടെയും ചികിത്സയുടെയും പണം ഞാൻ നൽകണമെന്നും എനിക്ക് മനസ്സിലായി [ ]
- ഞാൻ പഠനത്തിൽ നിന്നും പിൻമാറിയാലും എന്റെ മെഡിക്കൽ റിപ്പോർട്ട് ഈ പഠനത്തിൽ ഏർപ്പെട്ട ഡോക്ടർമാർക്കും സ്ഥാപനത്തിലെ എത്തിക്സ് കമ്മറ്റിയിലെ അംഗങ്ങൾക്കും പരിശോധിക്കാൻ അവകാശമുണ്ട്. ഇതിനായി എന്റെ സമ്മതം ഞാൻ കൊടുക്കുന്നു [ ]
- എന്റെ ഐഡന്റിറ്റി എവിടെയും വെളിപ്പെടുത്തുകയില്ല എന്നും ഞാൻ മനസ്സിലാക്കുന്നു [ ]
- ഞാൻ പൂർണ്ണമനസ്സാലെ ഈ പഠനത്തിൽ പങ്കെടുക്കുവാൻ സമ്മതിക്കുന്നു [ ]
- എനിക്ക് പഠനത്തെപ്പറ്റി കൂടുതൽ അറിയാനായി ബന്ധപ്പെടാൻ പ്രധാന ഗവേഷകന്റെ ഫോൺ നമ്പർ എനിക്ക് നൽകിയിട്ടുണ്ട് [ ]
- സമ്മതപത്രത്തിന്റെ ഒപ്പിട്ട ഒരു കോപ്പി എനിക്ക് കിട്ടി [ ]

പേര് :

ഒപ്പ് :

തീയതി :

സാക്ഷിയുടെ പേര് :

രോഗിയുമായുള്ള ബന്ധം :

ഒപ്പ് :

സമ്മതപത്രം ഒപ്പിടുവിച്ച വ്യക്തി

ഈ സമ്മതപത്രത്തിൽ ഗവേഷണത്തെപ്പറ്റിയുള്ള വിവരങ്ങൾ ആവശ്യാനുസരണം ഉണ്ടെന്ന് ഞാൻ സ്ഥിരീകരിക്കുന്നു. രോഗിയോട് ഈ പഠനത്തെ കുറിച്ച് ലഘുവായ ഭാഷയിൽ വിവരിച്ച് കൊടുക്കുകയും അവരുടെ സംശയങ്ങൾ ദൂരീകരിക്കുകയും ചെയ്തിട്ടുണ്ട്. പഠനത്തിനിടയിൽ ഉണ്ടായേക്കാവുന്ന അപകടങ്ങളെപ്പറ്റിയും ദൂഷ്യഫലങ്ങളെപ്പറ്റിയും രോഗിയോട് വിവരിച്ചിട്ടുണ്ട്. സംശയങ്ങൾ ചോദിക്കുവാൻ പ്രോത്സാഹിപ്പിക്കുകയും അവ ദൂരീകരിക്കുകയും ചെയ്തിട്ടുണ്ട്.

മുഖ്യ ഗവേഷകന്റെ പേര്

ഒപ്പ് : തീയതി

സാക്ഷിയുടെ പേര്

രോഗിയുമായുള്ള ബന്ധം

സാക്ഷിയുടെ ഒപ്പ്

PROFORMA

Title

A RETROSPECTIVE STUDY ON PREGNANCY IN MYASTHENIA GRAVIS

1. DETAILS OF PATIENT

Unique identification number :

Age :

Address :

Date of Recruitment :

Phone No:

Educational status : Primary/ High school/ University

Occupation :

2. Age of onset of symptoms :

3. Diagnosis by :

Test	Positive	Negative
Neostigmine test		
Acetylcholine Receptor Antibody		
Ice pack test		
RNS		

4. Status of Thymectomy: **If yes, Age at which Thymectomy done:**

5. Order of pregnancy: **Age:**

	PRE PREGNANCY STATE	1st TRIMESTER	2nd TRIMESTER	3rd TRIMESTER	3 MONTHS POSTPARTUM
Symptoms					
Highest MGFA Score					
Medications A) Steroids B)Azathioprine C) Neostigmine- D) Pyridostigmine- E) PLEX/IvIg					
Medical complication (If Any Specify)					
Pregnancy related complications PPROM-	NA				NA
Fetal Details Abortion- IUD- Stillbirth-	NA				NA

LABOUR:

MODE OF DELIVERY	Yes	No
VAGINAL **If yes,** -Spontaneous- -Forceps or vacuum assisted-		
LSCS If yes Indication:		

NEONATAL OUTCOME:

Preterm / Full term	
APGAR Score – 1min - 5min-	
Birth weight (kg)	
H/o NICU admission	Yes No
Duration of ICU admission (days)	
H/o - Mechanical ventilation -NIV	
Duration of mechanical ventilation or NIV (days)	
Duration of hospital stay (days)	
Transient neonatal MG	

MGFA CLASSIFICATION

MGFA Clinical Classification

Class I: Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.

Class II: Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class III: Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class IV: Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class V: Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

IEC CLEARANCE CERTIFICATE

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1347/FEBRUARY-2019 02.03.2019

Dr. Harikrishnan R
Senior Resident
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Harikrishnan,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "A RETROSPECTIVE STUDY ON PREGNANCY IN MYASTHENIA GRAVIS (IEC/1347)" on 16th February, 2019.

The following documents were reviewed:

Original submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 27.11.2018 with checklist*
2. *Forwarding Letter from HOD*
3. *TAC Approval Letter*
4. *IEC Application Form*
5. *Project Proposal*
6. *Proforma*
7. *Informed Consent Form and Information Sheet in English and Malayalam*
8. *CV of Principal Investigator and Co- Principal Investigators*

Revised submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 27.11.2018 with checklist*
2. *Forwarding Letter from HOD*
3. *TAC Approval Letter*
4. *IEC Application Form*
5. *Project Proposal*
6. *Proforma*
7. *Informed Consent Form and Information Sheet in English and Malayalam*
8. *CV of Principal Investigator and Co- Principal Investigators*

The following members of the Ethics Committee were present at the meeting held on 16th February, 2019 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Dr. Harikrishna Varma PR	Ph.D(Materials Science)	Male	Medical Technology	Yes
5.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
6.	Dr. S S Giri Sankar	LL.M. Ph.D.	Male	Legal Expert	No
7.	Dr. Aneesh V Pillai	BA. LLB (Hons.), LLM, Ph. D, SET (Law)	Male	Legal Expert	No
8.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
9.	Mr. Satheesh Chandran	MSW, PGDPM	Male	Lay person/ NGO/ Social Scientist	No
10.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
11.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

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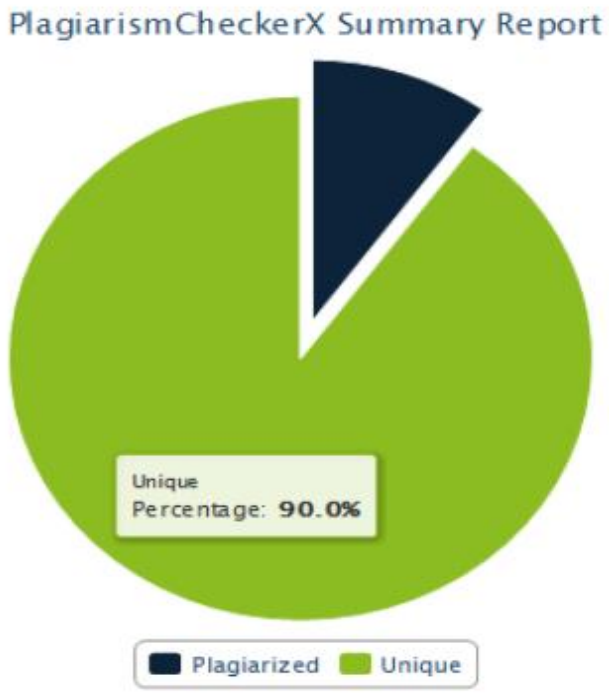

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