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Myasthenia gravis in pregnancy, disease course and outcome: Prospective observational study

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ABSTRACT

Background and objectives: Pregnant ladies with MG can have normal pregnancy and delivery, but the course is unpredictable, however, worsening of symptoms occurs more likely during the first trimester and puerperium. Our aim was to follow up pregnant women affected with myasthenia gravis (MG) to study the course of the disease, the extent of the disease sequelae, and the effect of different treatment modalities on maternal and fetal outcomes. *Methods:* We conducted a prospective observational study regarding treatment and follow-up for eighteen pregnant women with myasthenia gravis over a period of 20 years from 1999-2019 at the department of obstetrics and gynecology of a tertiary university medical city, in Saudi Arabia. The course of the disease, during pregnancy, mode of delivery, puerperium has been evaluated in addition to the state of the mother and the baby. *Results:* 66% of females had spontaneous vaginal delivery. Three only experienced relapse during pregnancy (16.6%), one patient (5.5%) experienced relapse in the puerperium, no patients had myasthenia crises, and six patients (33.3%) developed MG progression. One third of the patients were treated with cholinesterase inhibitors alone, and the rest received corticosteroids. Fourteen patients (77.7%) had a thymectomy. Four babies (22.2%) had transient neonatal myasthenia gravis. thymectomy in those females gave significantly different results, P=0.015. *Conclusion:* Myasthenia gravis can be managed well during pregnancy with safe and effective therapies. Caesarian section is recommended only for obstetrical reasons. Forceps and vacuum delivery are sometimes required. Myasthenia gravis during pregnancy can lead to serious life threatening conditions. An interdisciplinary approach is required for managing pregnant women with myasthenia gravis.

Keywords: Myasthenia; Gravis; Pregnancy; Disease; Course; Outcome; Single Arm; Open Labeled Trial.

1. INTRODUCTION

Myasthenia gravis (MG) is a chronic autoimmune disorder, characterized by varying degrees of weakness in the skeletal muscles of the body. It affects young women in the second and third decades of their lives overlapping with the child-bearing years (Strafford & Dildy, 2005, Ciafaloni & Massey, 2004). It is the most common primary disorder of neuromuscular transmission with a prevalence ranging from 25 to 125 cases per million of the general population (Gilhus, 2011). It may considerably affect the course of pregnancy and causes serious complications in both mother and infant (Ferrero, 2008, Ferrero, 2005).

Transient neonatal myasthenia gravis (TNMG) is a transitory form of myasthenia gravis occurring in 12-20% of infants born to myasthenic mothers (Ferrero, 2005). The disease presentation is varied, ranging from a mild to life-threatening situation. The course of the disease is variable and unpredictable during pregnancy and is due to the transfer of antibodies (IgG) from mother to the infant (Da Silva, 2011).

Treatment is frequently necessary before, during, and after pregnancy to ensure maternal and fetal well-being. However, knowledge of the potential effects of pregnancy on the course of MG and the use of immunosuppressive drugs during pregnancy is limited, rendering decision making difficult for both patient and the treating doctor (Berlet, 2012). Pregnancy does not worsen the long-term outcome of MG, but the disorder sometimes becomes manifested during pregnancy of post-partum (Hoff, 2007).

2. MATERIALS AND METHODS

From 1999 to 2019, we followed up to 81,489 pregnant females till delivery and furtherly during puerperium. 18 pregnant women was having and diagnosed with MG during that period. The incidence of MG was 0.022%. They delivered and treated at the department of Obstetrics and Gynecology, King Khalid University Hospital (KKUH), King Saud University, Riyadh, Kingdom of Saudi Arabia.

For those 18 women with MG, their obstetric history and the course of the current pregnancy, labor and puerperium were analyzed, as well as their infants during the neonatal period. Data were gathered in a delivery register. The diagnosis of MG was established at the neurology clinic. Regular check-ups during pregnancy were performed at the antenatal and the neurology clinics. Patient were classified according to their disease; ocular, facial, oropharyngeal, axial, or limb MG. Management was divided into two categories; medical cholinesterase inhibitors (e.g. pyridostigmine, prednisone, cyclosporine A) and surgical by thymectomy (partial or complete). The clinical status of MG was evaluated as follows: remission (complete or partial, but 75% already had thymectomy before pregnancy), relapse or crises. Neonatal data were also retrieved.

The women were examined before, during and after delivery. Information was obtained to address certain points like; gestational age, past medical history, current pregnancy, mode of delivery, and postpartum status. Follow-up of all neonates include the

gestational age, birth weight, Apgar score, admission to neonatal intensive care unit (NICU) and anti acetylcholine receptors (ACHR) antibodies titer.

Statistical analysis

Descriptive statistics for the numeric variables were presented as mean and standard deviation while that of the categorical variables were presented in the form of frequencies and percentages. The comparisons of means, mean differences and proportions, were calculated using McNemar test while the association between variables was done using Fisher's exact test. The statistical analysis was done using IBM SPSS statistics, version 26, and significance value was calculated at the level of 0.05.

3. RESULTS

The total number of patients was eighteen. The mean age of patients was 30.9±6.3 years, (range 22-43 years). Nine women (50%) were para I, three (16.6%) were - para V, one (5.5%) was para VI, three (16.6%) were para VII, two (11.1%) were para VIII and the mean parity was (4.25 ± 3.3), (Table 1).

The mean age at diagnosis was 25 ± 6.1 years (range 15-35 years). The mean gestational age at booking was 18 ± 9.6 weeks (range 7-37 weeks). The mean weight of women at booking was 63.2 ± 17 kg (range 40-93 kg) while it was 68.8 ± 18.2 kg (range 45-106kg) at the end of pregnancy (Table 1).

Table 1: Baseline demographic characteristics of the study group

demographic characteristics	Minimum	Maximum	Mean ± Std. Deviation
Age (years)	22.0	43.0	30.917 ± 6.388
Age at diagnosis of MG (years)	15.0	35.0	25.083 ± 6.1268
Gestational age at booking (weeks)	7.0	37.0	18.889 ± 9.6364
Gestational age at delivery (weeks)	36.0	42.0	39.0 ± 1.699
Weight at booking gestations (Kg)	40.0	93.2	63.27 ± 17.0514
Weight at end of pregnancy (Kg)	45.0	106.7	68.83 ± 18.2565
Height (cm)	147.0	166.0	157.1 ± 5.8775
Body Mass Index	16.33	41.68	28.268 ± 8.29
Parity (N)	1	8	4.25±3.3
Second stage duration in minutes (12 women)	10	25	17.5±4.3
Birth weight in kilograms for newborns	1.95	3.99	3.209 ± 0.653
Apgar score at 1 minute	5.0	8.0	7.70 ± 0.9487
Apgar score at 5 minutes	8.0	9.0	8.90 ± 0.3162

The mean body mass index (BMI) was 28.2 ± 8.2 (range 16-41). Six (33%) of the women had a history of previous abortion, one (5.5%) woman had a history ectopic pregnancy. There were four preterm labors and one postdate pregnancy. The mean duration of the seven term pregnancies was 39.4 weeks±1.6 (range 36-42 weeks). Two women (11.1%) had gestational diabetes mellitus (GDM) managed on diet, only one (5.5%) had pregnancy induced hypertension (PIH) and was on alpha methyl dopa (aldomet) and one had hypothyroidism on thyroxine.

Twelve labors (66.7%) were completed vaginally. The vacuum extractor was used four times (22.2%) to shorten the second stage as recommended by the neurologist. Six pregnancies (33.3%) were terminated by caesarean section (CS) because of fetal distress. The mean duration of the second stage of labor for 12 women was 17.5 minutes (range 10-25 min) two women had epidural anesthesia (11.1%) without complications. Generally the course of the disease was tolerated by all patients, however nine women (50%) had MG remission, partial or complete. Three women (16.6%) developed relapse during pregnancy and one (5.5%) had relapse in the post-partum period.

Six patients (33.3%) developed MG progression. Five patients (27.7%) developed the ocular form of MG, five patients (27.7. %) developed the facial form, three women (16.6%) developed the oro-pharyngeal form of MG, two women (11.1%) developed the limb form and one woman (5.5%) had axial muscle MG. Only one woman (5.5%) was free of symptoms. Six patients (33.3%) were treated with an acetylcholine esterase inhibitor (pyridostigmine bromide) only, and the other twelve women (66.6%) were treated with pyridostigmine bromide together with corticosteroids (prednisone).

Complete thymectomy had been performed for fourteen women (77.7%), eight of them (44.4%) had thymectomy prior to pregnancy. Twelve (66.6%) women improved after thymectomy. Table 2 shows the histopathology of the thymus gland tissue. The acetyl choline receptors antibodies were assayed in just twelve (66.6%) patients. Ten (55.5%) of them were sero-positive and two (11.1%) were sero-negative. Electromyogram (EMG) was used to assess eight (44.7%) women. Edrophonium test was positive in six (33.3%) and neostigmine test was positive in four (22.2%) women. The mean newborn's body weight was 3.2 ± 0.6 kg (mean 1.85-3.99 kg). Apgar scores were 7.7 ± 0.9 and 8.9 ± 0.3 at one and five minutes respectively (Table 1, figures 1-4).

Table 2: Histopathology findings of thymus gland tissue in the fourteen thymectomized women

Histopathology	No.	(%)
Thymus involution	2	14.2
Hyperplasia	7	50
Nodular Cystic Degeneration	2	14.2
No trace	3	21.6

Eleven (61.1%) were admitted to the neonatal Intensive Care Unit (NICU). Only one (5.5%) infant developed neonatal crisis, however, neonatal signs appeared in four (22.2%) infants. One (5.5%) infant developed anti Ach-R antibodies. No nursing data were available.

Table 3: Difference between the observed means in the sampled population

Variables	Mean ±SD	Difference	Standard error	95% CI	t-statistic	Significance level (2 tailed)
Mean age of patients	30.917 ± 6.388	-5.9	2.067	-10.1005 to -1.6995	-2.854	0.0073*
Mean age at diagnosis	25.083 ± 6.1268					
Mean Gestational age at booking (weeks)	18.889 ± 9.6364	20.1	2.306	15.4239 to 24.7981	8.720	0.0001*
Mean Gestational age at delivery (weeks)	39.0 ± 1.699					
Weight at booking gestations (Kg)	63.27 ± 17.0514	5.56	5.888	-6.4060 to 17.5260	0.944	0.3517
Weight at end of pregnancy (Kg)	68.83 ± 18.2565					

*Two tailed p value was considered significant at level of <0.05

The result, P=0.015, in table 3, 4, indicates that the thymectomy in those females gave significantly different results. Pregnant ladies with MG can have normal pregnancy and delivery, as shown in table 5 but the course is unpredictable, however, worsening of symptoms occurs more likely during the first trimester and puerperium. 66% difference, 95% CI was (34.2806- 81.6408) and P value =0.0001. Myasthenia gravis can be managed well during pregnancy with safe and effective therapies. Caesarian section is recommended only for obstetrical reasons. Forceps and vacuum delivery are sometimes required. 32.7 % difference, 95% CI was (0.3161-56.9509), P value = 0.0530. Myasthenia gravis during pregnancy can lead to serious life-threatening conditions. An interdisciplinary approach is required for managing pregnant women with myasthenia gravis.

Table 4: Relationship between the effect of thymectomy and patients' improvement using Fishers' Exact test with small number of expected frequencies, to determine the probability of obtaining the observed result or a more extreme result

Variables		Patients improved, N (%)		Total	Exact probability	(two-sided) P-value
		Yes	No			
Patients underwent thymectomy, N (%)	Yes	12(66.6)	2(11.1)	14(77.7)	0.0441	0.015*
	No	1(5.5)	3(16.6)	4(22.2)		
Total		13(72.2)	5(27.7)	18(100)		

*Two tailed p value was considered significant at level of <0.05

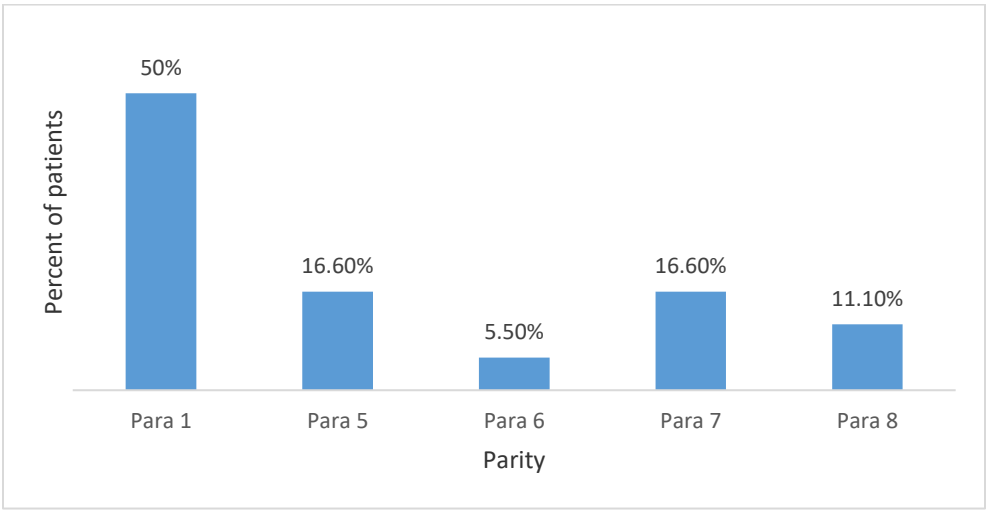

Figure 1: Parity among the patients

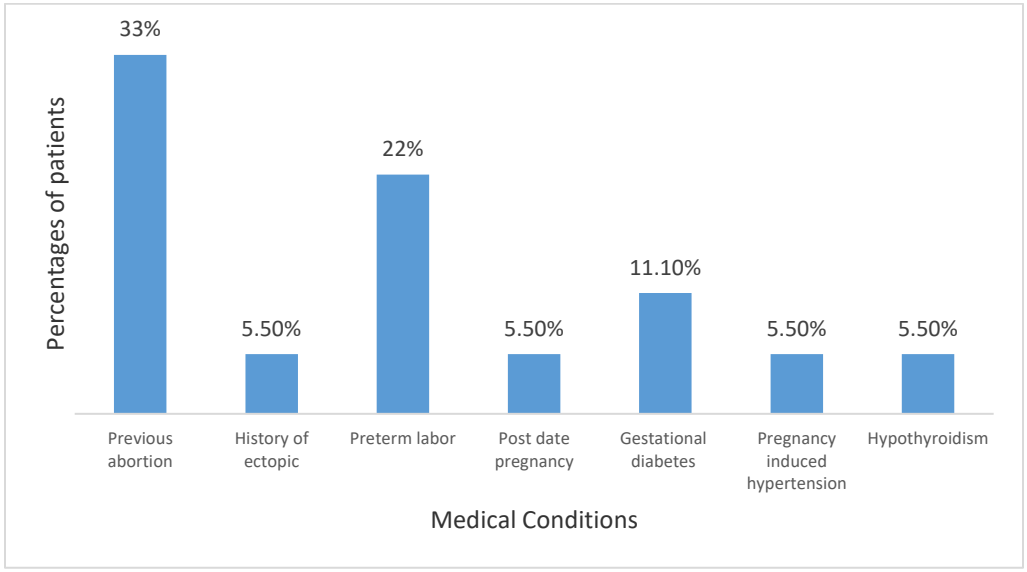

Figure 2: Clinical characteristics of the patients

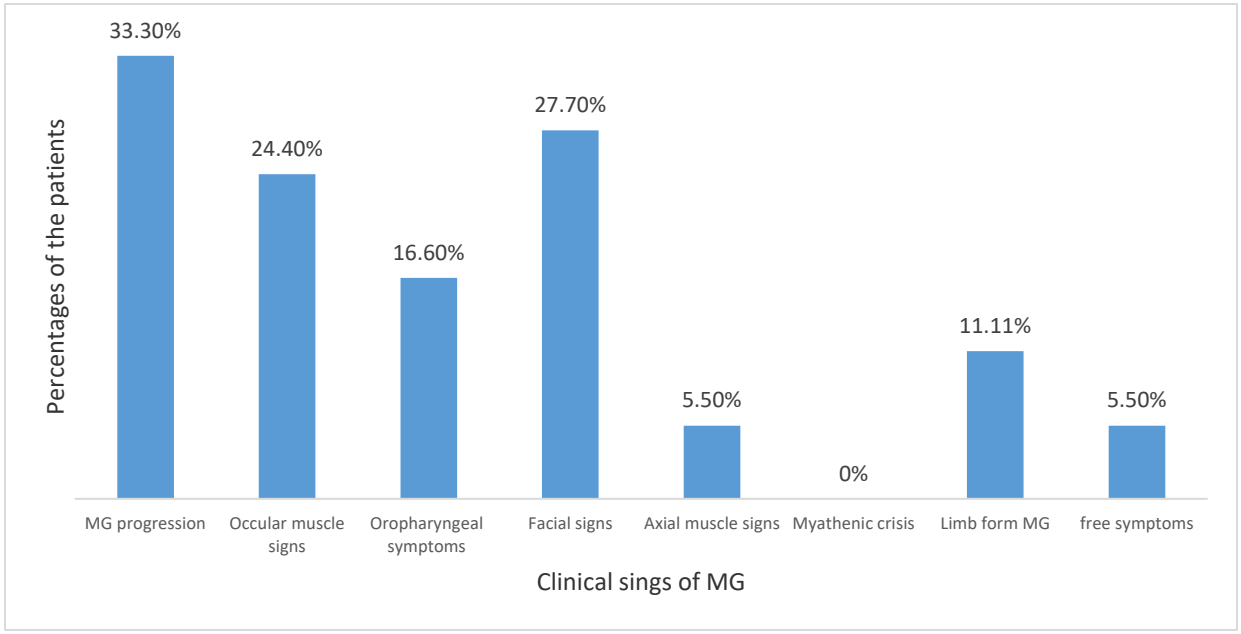

Figure 3: Clinical signs of myasthenia gravis

Table 5: Comparison between myasthenia gravis patients underwent CS, and had relapse during pregnancy and postpartum period

Variables, N (%)			Difference	95% CI	Test value	(two-sided) P-value
Mode of delivery	SVD	12(66.7)	33%	0.6047- 57.1881	3.812	0.050*
	IVD	4(22.2)	ref	ref	ref	ref
	CS	6(33.3)	32.7 %	0.3161-56.9509	3.743	0.0530*
Relapse during pregnancy or after delivery	Yes	4(22.2)	66%	34.2806-81.6408	15.4	0.0001*
	No	14(77.7)	ref	ref	ref	ref

SVD: spontaneous vaginal delivery, IVD: instrumental vaginal delivery, CS: cesarean section *Two tailed p value was considered significant at level of <0.05

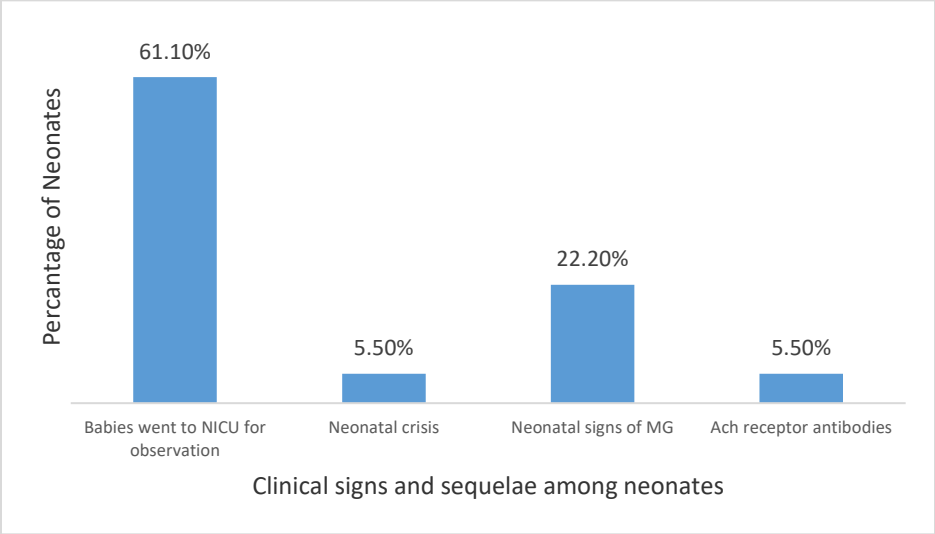

Figure 4: Neonatal signs of MG

4. DISCUSSION

Recent general estimations of myasthenia gravis suggest 20 cases of myasthenia gravis per 100,000 (Behin et al., 2008). Estimations of worldwide prevalence of myasthenia gravis vary greatly due to regional discrepancies. The incidence of myasthenia gravis in gestation is reported at 1 in 20,000. Transitional neonatal myasthenia gravis about 10-15% of the pregnancies of women with myasthenia gravis happen (Alabdali, 2014). The literature describes the clinical course of pregnant women with myasthenia gravis consist mostly of single case reports and case series.

The pathogenesis of myasthenia gravis is unknown, but the increased frequency of other auto antibodies and auto-immune diseases together with a positive effect of immunosuppressive therapy suggest as immunological cause (Ferrero, 2008, Behin et al., 2008). Myasthenia gravis affects the neuromuscular junction due to the production of anti-acetylcholine receptor antibodies (AChR-abs). These are IgG antibodies and may cross the placenta causing transient neonatal myasthenia gravis (Da Silva, 2011).

Thymus gland antibodies are clearly associated with MG. Ten percent of patients with MG have a thymus tumor and 70% have hyper-plastic changes (Karelis et al., 2019). The thymus plays a key role in the pathological breakdown of self-tolerance leading to MG. Women of child-bearing age who have MG have an enlarged thymus and circulating AChR-abs in most cases. However, thymectomy during pregnancy has no role because of its delayed effect and possible surgical risk after thymectomy (De Meel, 2019), clinical remission has been shown to occur in 35% to 45% of patients (Gilhus, 2011). The maximal favorable response generally occurs 2-5 years after surgery. Prior to planning a pregnancy, women should participate in an informed decision making regarding the medical management and maternal and fetal risks involved. Recommendations however should be based on the severity of MG (Karelis et al., 2019).

Corticosteroid therapy is effective in most patients with MG. Marked improvement of symptoms occurs in 75% of patients treated with prednisolone. Inappropriately, relapse seems to be upheld only if the patient treated for a long time with steroids, however exacerbations may occur on sudden abrupt steroid withdrawal. For these reasons, pregnant MG patients on corticosteroids should be maintained on them throughout pregnancy and the postpartum period. It is safe during pregnancy (Ferrero, 2005)

Azathioprine reverses symptoms in most patients but the effect is delayed by up to 4 to 8 months. Patients who fail to respond to corticosteroids therapy may respond to azathioprine and the reverse is also true. Azathioprine crosses the placenta, but has no teratogenic effect. Babies born to mothers receiving azathioprine may have an increased risk of myelo-suppression and immune suppression (Ciafaloni & Massey, 2004). Cyclosporine A inhibits predominantly T-lymphocytes-dependent immune responses and is sometimes beneficial in treating MG. Cyclosporine A may increase the risk of having a low birth weight baby, prematurity and spontaneous abortion (Wang, 2017).

Methotrexate should not be used to treat MG in women of childbearing age, because it has teratogenic effect on the fetus. Cyclophosphamide is usually used in few cases of MG refractory to all other therapeutic modalities. Plasmapheresis, is very effective treatment when short-term benefit is critical (Wang, 2017). Plasmapheresis can result in premature delivery, allergy, transitory cardiac arrhythmias and obscured vision. Intravenous immune globulins (IVIG) have non-specific suppressive effect on the immune system. Although the safety of this therapy during pregnancy has not been established, this treatment has proved to be effective and safe for deteriorating MG during pregnancy

Pregnancy does not worsen the long-term outcome of MG (Da Silva, 2011). The course of the disease is a variable and unpredictable and can change during the current pregnancy and even can change during subsequent pregnancies. The most critical periods for myasthenia gravis exacerbation occur during the first trimester and the first postpartum period.

Therapeutic abortion has shown variable results for disease course, with flares resulting from anesthesia and the stress of surgery. Myasthenia gravis is not an indication for the termination of pregnancy. The perinatal death rate is unaffected by myasthenia gravis, but the death rate due to fetal abnormalities is increased (Berlet, 2012). About 10-20% of infants born to myasthenia gravis women show signs of neonatal myasthenia gravis caused by passive transfer of antibodies from mother to child (Da Silva, 2011).

An increased risk of pre-eclampsia has not been demonstrated among myasthenic patients. There have only been five cases of pregnancy complicated by MG and pre-eclampsia reported in the literature (Gilhus, 2011). Fetal assessment tests that rely on alterations of fetal movement or response to the heart rate to wikiing are not usually accurate in myasthenia gravis. This comprises the patient's awareness of wikiing. Polyhydramnios resulting from impaired fetal swallowing has been described in several case reports (Gilhus, 2011). In severe cases, fetal arthrogryposis multiplex congenital may be observed in pregnant myasthenic patients.

Passive placental transfer of ant acetylcholine receptor IgG can be responsible for symptoms in the fetus prenatally and may cause transient neonatal MG after delivery. Approximately 10% to 20% of infants born to myasthenic mothers experience transient neonatal MG. the disease course is short lived with onset of manifestations approximately 12 hours after delivery and resolution after 3 months. The early onset may be related to passive transfer of anticholinesterase drugs or to high levels of AFP. Breast feeding is considered safe for unaffected infants (Gilhus, 2011, de Meel, 2020).

Concerning the mode of delivery, most labors can be safely completed vaginally. The uterine contractions of labor occur normally in the myasthenic mother (Strafford & Dildy, 2005, de Meel, 2020). Forceps delivery and vacuum extraction may be needed. Choline esterase inhibitor medications should be. Surgical delivery poses a multitude of risks for myasthenic patients and should be reserved for those with severe myasthenic exacerbations, myasthenic crisis and obstetrical indications (Gilhus, 2011, Beecher, 2017).

Analgesia is advised to reduce physical and emotional stress. Epidural anesthesia should be used both in vaginal and operative delivery to decrease the requirement of systemic medications (Bourque, 2016). Breast feeding is not contraindicated in women with MG. AChR antibodies may pass to the infant through breast milk and may potentially enhance neonatal myasthenia gravis (Adiao, 2020).

Transient neonatal myasthenia gravis (TNMG) is a syndrome that affects 10% to 20% of newborns of myasthenic mothers and occurs shortly after birth (Chieza, 2011). The disorder usually begins 12 to 48 hours after birth and lasts 10 days to 15 weeks. Myasthenic women who desire children and is should be emphasized that the absence of MG symptoms in the mother does not guarantee the birth of a normal newborn (Briggs, 2008). Because human breast milk confers many benefits for the infant, advice to mothers should review the risk of the received drugs against the disadvantages of formula feeding. Some mothers also find that loss of sleep from night feeding worsen symptoms of MG and choose not to breast feed (Ostensen et al., 2008).

This study showed the rate of MG in pregnancy is comparable to other regions. The age of diagnosis was later but had no effect on the course of the disease. The mean parity was 4 + 3.3 which is higher than other societies but is normal in Saudi Arabia (Gold, 2008). The mean BMI was 28.2 + 9.2, which was higher than normal. Although 50% of our cases had history of abortion in previous pregnancies, they had no abortions in the current one. In this study one patient had a cesarean section (8.3%, eight (66.7%) were delivered vaginally and two (16.7%) by vacuum extraction (Ibrahim, 2013).

5. CONCLUSION

Myasthenia gravis had little effect on the progress of labor, body weight and Apgar scores. Nevertheless Eleven babies (61.1 %) were admitted to NICU, but neonatal symptoms had appeared in four (22.2%) babies. There were no congenital abnormalities in any of the infants. Pyridostigmine alone was the drug of choice for symptomatic treatment of MG, occasionally it was combined with corticosteroids. Complete thymectomy done before pregnancy in fourteen (77.7%) patients had an effective role in the management of MG.

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Author Contributions

Waleed, Wael and Ahmed conceived the presented idea. They developed the theory and performed the computations. They verified the analytical methods. They encouraged, to investigate and supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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Conflict of Interest

The authors declare that there are no conflicts of interests.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study.

Ethical approval

The study was approved by the Medical Ethics Committee of King Saud University (ethical approval code: JH.QWF-IU/908-72).

Data and materials availability

All data associated with this study are present in the paper.

Peer-review

External peer-review was done through double-blind method.

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