Myasthenia Gravis with Subsequent Premature Ovarian Insufficiency: A Case Report

Cialuj Teza Agbayani-Cruz, MD, FPOGS, FPSRM[1]* and
Maria Antonia E. Habana, MD, MSc, FPOGS, FPSRM, FPSGE[2]
[1]Department of Obstetrics and Gynecology, Angeles University Foundation Medical Center
[2]Department of Obstetrics and Gynecology, UP Manila – Philippine General Hospital

The incidence rate of Myasthenia Gravis coexisting with other autoimmune diseases is approximately 8.7 – 25%, but it is rarely associated with premature ovarian insufficiency (POI) with only less than 1% of women affected. This is a case of premature ovarian insufficiency in a 29 year old woman diagnosed with Myasthenia Gravis, who presented with lower extremity weakness and experienced two episodes of myasthenic crisis requiring thymectomy. Three years after, she noted oligomenorrhea that quickly progressed to amenorrhea. Extensive immunologic and genetic investigative studies showed no identifiable cause for the POI, except for its close temporal relationship with the occurrence of Myasthenia Gravis. The patient has been responsive to hormone replacement and immunomodulation therapy, and has not developed any further episodes of myasthenic crisis. A review of seven other reported cases describing a similar condition was also included in the discussion.

Key words: Myasthenia Gravis, premature ovarian insufficiency, autoimmune disorders

Introduction

Myasthenia gravis is characterized by antibody-mediated autoimmune attack against acetylcholine receptors (AChRs) at the neuromuscular junction. While it is commonly associated with other autoimmune diseases, its occurrence with premature ovarian insufficiency (POI) is rarely reported.[1] Currently, eight cases are published worldwide, including this case.

This report highlights a very rare case of Myasthenia Gravis coexisting with premature ovarian insufficiency. It is very important for clinicians to become aware of this association, in order to identify women at risk of POI and prevent long-term effects by providing timely interventions for fertility preservation. It has also been reported that early intervention using immunotherapy may possibly restore fertility in affected women. This report describes how clinical management should be done, including the essential diagnostic studies, therapeutic strategies, proper counseling and close monitoring.

The Case

A 29 year old nulligravid had regular menstrual cycles until she noted amenorrhea 3 years after being diagnosed with Myasthenia Gravis. Five years prior to consultation, patient started to experience progressive lower extremity weakness. She spontaneously regained complete lower extremity strength after one month. Three years prior to consultation, she had progressive upper extremity weakness accompanied by dysarthria, diplopia, ptosis, fatigue, and dyspnea. She was diagnosed with Myasthenia Gravis, which was confirmed with electromyography showing decrements of muscle action potential and an elevated acetylcholine

*For correspondence: cialujteza@gmail.com

receptor (AChR) antibody result (289 nmol/ L [cut-off: >40]). A month into Pyridostigmine therapy, she experienced myasthenic crisis during menses, presenting as generalized weakness and respiratory distress, and required mechanical ventilation. She was given Pyridostigmine 240 mg and Prednisone 30 mg, tapered down over three months. During this time, patient also noted onset of oligomenorrhea, noting scanty to light menstrual bleeding, which persisted for three months, until she eventually experienced amenorrhea.

In a span of two years, she experienced two more episodes of myasthenic crisis that necessitated intubation. This medical crisis required her to undergo thymectomy. She reported good control of Myasthenia Gravis post-operatively. Histopathologic examination of the thymus gland showed benign tissues (Figure 1). She was maintained on Prednisone 10mg, Pyridostigmine 240mg, and Azathioprine 50mg post-operatively.

Amenorrhea persisted for three years prior to consult. Patient did not experience hot flushes, mood swings, sleep disturbances, vaginal dryness or pruritus, nor skin dryness, except for an 8-kg weight gain. No neuromuscular deficits were noted. She had adult secondary sexual characteristics and normal pelvic findings.

At the time of consult, she was asymptomatic except for amenorrhea. Pregnancy test was negative.

Premature ovarian insufficiency (POI) was diagnosed when two measurements of serum follicle stimulating hormone (FSH) were in the menopausal range: 85.63 mIU/ mL on initial visit and 67.57 mIU/ mL eight weeks after. Estradiol was likewise low (43 pg/mL). Prolactin and thyroid function tests were normal. Transvaginal ultrasound showed small-sized uterus with linear endometrium and atrophic ovaries (Figure 2). Cranial MRI did not show any mass or lesion. Karyotyping showed normal female karyotype (46,XX) with no chromosomal abnormality. Fragile X mental retardation 1 (FMR1) gene premutation screening showed no expression of the fragile site at band Xq27.3 (FRAXA) which rules out a genetic cause of the POI. Lastly, to rule out autoimmune causes, baseline autoimmune screening showed negative results for both anti-ovarian antibodies (AOAs) (2.19 RU/mL [cut-off:>10.0]) and thyroid peroxidase antibodies (TPO Ab) (0.23 IU/mL [cut-off:>5.61]), but was positive for AChR Ab (289 nmol/L [cut-off: >40]), which play a role in both Myasthenia Gravis and POI.

Tests to evaluate long-term consequences of POI were done next. Dual energy x-ray absorptiometry (DEXA) showed osteoporosis (T-score -4.2). Lipid profile and fasting glucose were normal.

Treatment

The clinical implications of POI, effect on fertility, and importance of hormone replacement therapy (HRT) was discussed thoroughly with the patient. She was given continuous oral estrogen (Estradiol valerate 2 mg) and cyclic oral progesterone (Dydrogesterone 10 mg). For Myasthenia Gravis,

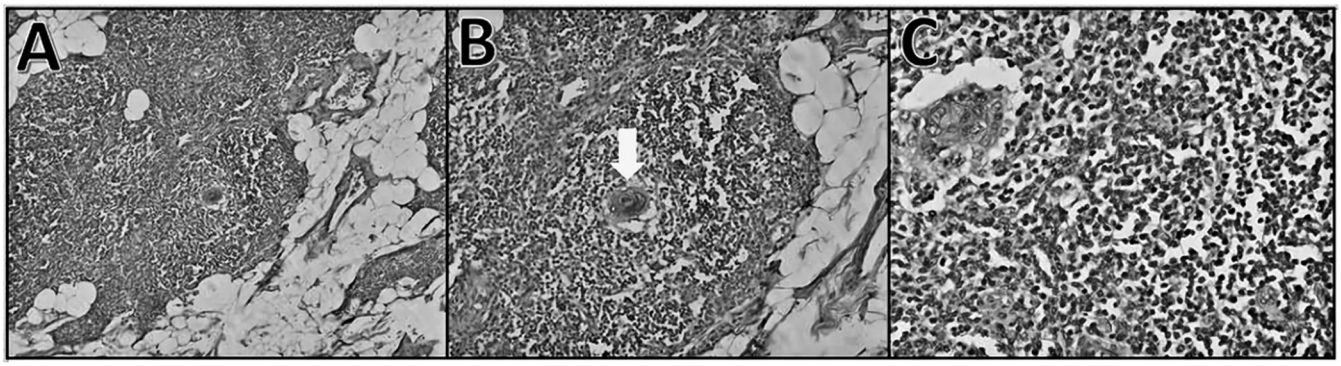

Figure 1. Microscopic images of the patient's thymus. (A) Scanning view shows inflammatory cells arranged in sheets and/or lobules, monomorphic looking with intersecting fibrous septa and surrounded by mature adipose tissues. (B) Low power view shows monomorphic-looking inflammatory cells arranged in sheets and/or lobules with pink keratinized lamillated structure termed as Hassall's corpuscles (white arrow). (C) High power magnification shows monorphic-looking inflammatory cells mostly composed of lymphocytes. No atypia, pleomorphism, or blast was noted.

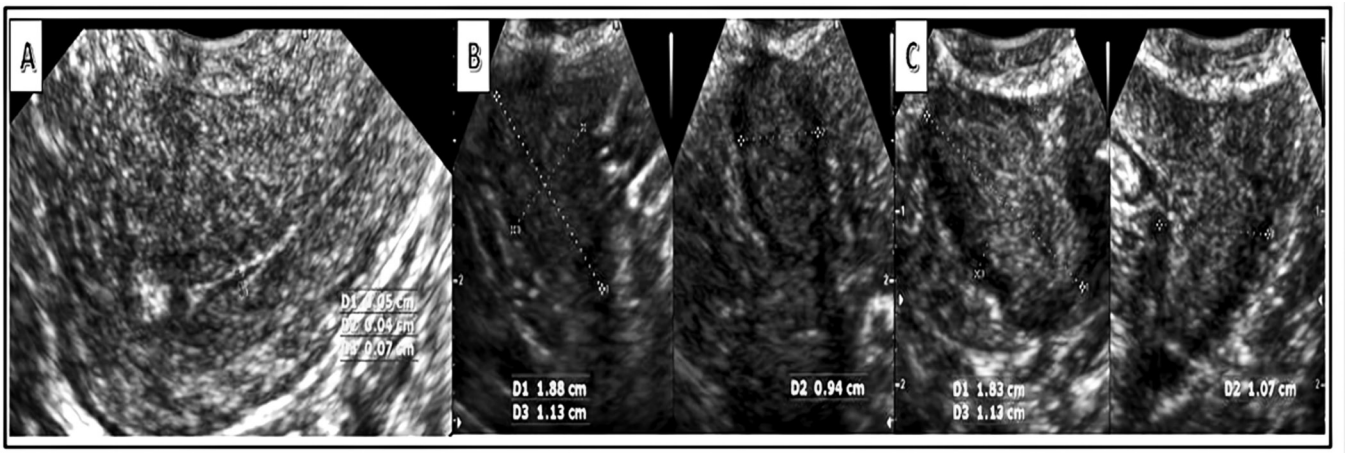

Figure 2. Transvaginal ultrasound images. Transvaginal ultrasound revealed a small-sized uterus with linear endometrium (A). The right (B) and left (C) ovaries were small with no antral follicles seen.

she was maintained on Pyridostigmine 240 mg, Prednisone 10 mg and Azathioprine 50 mg. Since estrogen can exacerbate myasthenic crisis, doses were adjusted to achieve symptom control and maintain bone health while monitoring for Myasthenia Gravis. Baseline cardiovascular risk assessment was low. In addition to HRT, she was given calcium and Vitamin D supplementation for osteoporosis, advised fall precautions, and referred to Orthopedics. Lifestyle modifications like healthy weight maintenance, avoidance of cigarette smoking and heavy alcohol intake, and regular non-weight-bearing exercises were discussed.

The patient was counselled about the possibility of spontaneous ovulation and since HRT is not contraceptive, other forms of contraception were advised should she not wish to conceive. Other fertility options include oocyte or embryo donation but are currently not allowed in the country.

She was referred to Psychiatry to address the anxiety from receiving the diagnosis and was informed of available support groups.

Outcome and Follow-up

The patient was monitored until a maintenance dose of HRT was established. Regular menses resumed after 3 months. Myasthenia Gravis medications were downtitrated every 3 months. No exacerbations were noted. Thereafter, symptom control and complication screening were done annually.

Discussion

Women constitute 78% of those affected by autoimmune disorders. Hormonal fluctuations, immune polarization, and the transition states of puberty, pregnancy and menopause increase susceptibility of women to autoimmune disorders. Interactions between estrogens, androgens, leptin and prolactin, and an interplay between Th1 and Th2 immune responses allow susceptible women to reach autoimmunity tipping point.[1]

Myasthenia Gravis (MG) is a neuromuscular disorder characterized by a decrease in AChRs at the neuromuscular junction due to antibody-mediated autoimmune attack. AChR Ab are induced by interaction of myeloid cells, lymphocytes, interdigitating cells, and epithelial cells in the thymus. Although acetylcholine (ACh) is released normally, the small end-plate fails to trigger muscle action potentials causing fewer and fewer activated muscle fibers, resulting in weakness and fatigue.[1]

While MG associated with autoimmune disorders like Hashimoto's thyroiditis, Graves' disease, rheumatoid arthritis, and lupus erythematosus has an incidence of 8.7 – 25%, it is rarely associated with POI. On the other hand, 20% of POI patients have a history of other autoimmune disorders, with autoimmune thyroid disease being the most common. In these patients, there is ovarian resistance to hormonal activation as autoantibodies competitively antagonize FSH or luteinizing hormone (LH). In POI with MG, secondary amenorrhea occurs before or

alongside MG in 5 of the 8 cases (71%). Uncontrolled thymic expression of antigens specific to ovaries contribute to ovarian autoimmune disease.[3] In our index patient, SLE in a cousin increases her risk for autoimmune disorders. POI occurred two years after the first myasthenic crisis. The temporal relationship and pathogenic link of these two conditions are not very clear.

POI is a clinical syndrome in women aged less than 40 years characterized by loss of ovarian activity. Its prevalence is approximately 1%. Oligomenorrhea or secondary amenorrhea is present for 4 months with elevated serum FSH level (> 25 IU/L) on two occasions, 4 weeks apart. Initial investigative measures include chromosomal analysis, Fragile-X premutation testing, and screening for adrenocortical and thyroid peroxidase antibodies (TPO Ab).[4] If POI coexists with an autoimmune disorder, autoantibody screening is indicated.[5] In this patient, TPO Ab levels were low, but AChR Ab levels were high.

Different autoantibodies are seen in different types of autoimmune POI. First are steroid cell antibodies that attack steroid-producing cells of the ovary, placenta, and adrenal cortex. Second are TPO Ab which cause hypothyroidism. Interestingly, thyroid autoimmunity is the most common (25-60%) endocrine autoimmune disorder seen with POI. Third are antiovarian antibodies (AOAs) which appear in 30-60% of POI women before onset of clinical symptoms. AOAs also signify future ovarian failure in patients with unexplained infertility.[6]

Other autoantibodies that target ovaries and are found in isolated POI include 3β-hydroxysteroid dehydrogenase autoantibodies, gonadotropin receptor autoantibodies, zona pellucida autoantibodies, and anti-oocyte cytoplasm antibodies. This signify a shared autoimmune response between "sister organs" like the ovaries, thyroid and adrenals.[6] The case presented was negative for both AOA and TPO Ab. Steroid cell antibodies were not available in the country.

Patients who have POI with MG are fewer than 1%. There are 8 documented cases of MG accompanied by POI and are summarized in Table 1. The two disorders are either simultaneously present or occur a few years apart. The co-existence of MG and POI represents a disorder of impaired immunoregulation involving the thymus gland, AChRs, and estrogen. Both diseases are associated with carriage of HLA antigen DR3. Defective epithelial expression of major histocompatibility complex class II molecules and autoimmune regulator gene leads to T cell over-reactivity. Myoid cells within the thymus express AChRs that trigger autoimmune reaction by becoming an autoantigen. T cells that mature in the thymus gland produce antibodies against these.[1] Thymectomy has been reported to cause resumption of ovarian function in one case.[7] ACh and its receptors are also found in the ovary and are attacked by the same AChR Ab that affect the NMJ.[3] This cross-reactivity with antibodies to the AChR in muscles and the ovaries could explain POI associated with MG. Estrogen promotes AChR-specific Th1 cell expansion and the development of pathogenic autoreactive B cells. It also increases activity of acetylcholinesterase enzyme, causing increase in the breakdown of ACh.[8] This mechanism explains MG experienced by the patient during her menses, and a report of MG after initiation of HRT in another patient.[9]

The eight cases reported were women in the first decade of their reproductive debut with ages ranging from 15-27 years. Majority (50%) manifested with MG first, followed by POI after several years, three cases (37.5%) had POI earlier than MG, while one case was simultaneously diagnosed with MG and POI. All cases showed hypergonadotrophic hypogonadism and ovarian failure in their hormone assays. Six of the cases (75%) were AChR Ab positive, while this was not tested in the other two cases. Other antibodies were anti-LH antibody (12.5%), AOA (12.5%), and thyroglobulin antibody (12.5%), each occurring solely in three separate cases. MG patients have also been reported to have an increased number of estrogen receptors alpha in thymocytes and peripheral T lymphocytes which could propagate the development of POI. Although ovarian biopsy is not recommended for confirmation of autoimmune POI, one case underwent ovarian biopsy and showed lymphoid oophoritis.[3] Seventy-five percent of the reported cases of MG with POI were from Asia.

A notable case with similar course as the patient was reported in 2011 by Cakir et al.[7] Both cases presented with generalized MG and developed POI 2-3 years after. No other autoantibodies were noted except for AChR Ab. Both cases underwent thymectomy. The former experienced spontaneous resolution of menstrual cycles after

Table 1. Summary of the cases with myasthenia gravis with POI. (Adapted from Liu, et al. 2018)[3]

Patient profile	Year of Study							
	1981 (Kuki et. al., 1981)[10]	**1993 (Chung et. al., 1993)[11]**	**2004 (Ryan et. al., 2004)[12]**	**2010 (Li et. al., 2010)[9]**	**2010 (Dong et. al., 2010)[13]**	**2011 (Cakir et. al., 2011)[7]**	**2018 (Liu et. al., 2018)[3]**	**2021 (Agbayani-Cruz and Habana, 2021)**
Age at Onset	19	26	27	19	15	18	23	21
Clinical presentation	Diplopia Fluctuating weakness Bulbar muscle weakness	Ptosis Easy fatigability Upper extremity weakness	Difficulty with fine motor on the right hand Bulbar muscle weakness	Ptosis Easy fatigability Limb muscle weakness Respiratory muscle weakness	Generalized myasthenia gravis	Generalized myasthenia gravis	Ptosis Dysarthria Dysphagia Easy fatigability	Limb muscle weakness Diplopia Ptosis Easy fatigability Respiratory muscle weakness
Temporal relationship the two diseases	POI occurring 2 years after MG	Diagnosed with MG followed by POI shortly	POI occurring 12 years before MG	Simultaneous occurrence	POI occurring 3 years earlier than MG	POI occurring 3 years after MG	POI occurring 1 year earlier than MG	POI occurring 2 years after MG
Hormonal Assays	Elevated FSH Reduced serum estradiol	Elevated FSH Reduced serum estradiol	Elevated FSH Reduced serum estradiol	Elevated FSH Reduced serum estradiol	Elevated FSH Reduced serum estradiol	Elevated FSH Reduced serum estradiol	Elevated FSH Reduced serum estradiol	Elevated FSH Reduced serum estradiol
Auto-antibody screening								
MG	N/A	N/A	(+) AChR Ab	(+) AChR Ab	(+) AChR Ab	(+) AChR Ab	(+) AChR Ab	(+) AChR Ab
POI	Anti-LH Ab (+)	N/A	N/A	(+) AOA	N/A	(-) AOA (-) TGAb (-) TMA (-) Anti-21-hydroxylase enzyme Ab	(-) ANA (+) TGAb (+) TMA	(-) AOA (-) AntiTPO Ab
Ovarian biopsy	N/A	N/A	(+) lymphoid oophoritis	N/A	N/A	N/A	N/A	N/A

thymectomy without HRT. Authors suggested HRT discontinuation to check for ovarian recovery in patients with MG after thymectomy.[7]

The goals of therapeutic hormonal regimens are to relieve menopausal symptoms and to protect against the consequences of estrogen deficiency. HRT should be continued until at age 52 years, the average age of menopause, and is aimed to achieve physiological estradiol levels (50-100 pg/ml).[15] Continuous estrogen replacement is required, supplemented with cyclical progesterone for endometrial protection from endometrial hyperplasia and neoplasia.[4] Sometimes, estrogen replacement in POI result in recovery of ovarian function by restoring receptor sensitivity to gonadotropins, heralding folliculogenesis. This explains spontaneous conception in 5% of cases.[4,6]

Immunomodulating therapy for MG may help restore menses, but its effect is related to the duration of amenorrhea. If the duration of amenorrhea is long, this can lead to complete uterine atrophy, which renders resumption of menstruation difficult.[16]

Future pregnancies are achieved through in-vitro fertilization using donor oocytes or embryos.[4] The role of in vitro activation, where mature oocytes are developed from remaining primordial follicles, is still experimental.[17] If the onset of the autoimmune disorder is identified, an immediate course to perform ovarian tissue cryopreservation should be discussed. Stem cells have been successfully differentiated from adult human ovarian cortex and may open a new chapter in treating POI-related infertility.[18]

Monitoring for long-term sequelae of POI include annual blood pressure, fasting blood sugar and lipid profile screening, and DEXA bone scan every 5 years.[4] Psychological support is essential because the significant morbidities of these two diseases increase the risk for depression.[6]

Future research is aimed at identifying the autoimmune link, to reverse or slow down destructive effects of autoimmune disorders to ovarian function, and to identify women with MG who are at most risk for autoimmune POI. Longer follow-ups will allow monitoring of the two diseases' progression and interplay.

Conclusion

Women diagnosed with autoimmune disorders should be evaluated for POI. Menstrual characteristics should be monitored for irregularity and change in volume. A baseline hormone profile should be obtained and re-assessed if signs of POI surface. If POI is diagnosed early, fertility preservation may be offered.

The management of women with MG and POI requires a multi-specialty approach. There is a need to balance immunomodulating therapy for MG and hormone replacement therapy for POI, while being vigilant of cardiovascular disease, stroke, cognitive decline and osteoporosis. Quality of life, future fertility and psychologic issues should also be addressed.

Prospective observational studies should look into the relationship of MG and POI and identify women at risk of having both diseases.

Patient's Perspective

Three months after undergoing thymectomy, I decided to consult because my menstruation stopped suddenly months after I was diagnosed with Myasthenia Gravis. It's very hard for me to accept the fact that I can no longer be able to produce eggs and that my Dexa Bone Scan result showed Osteoporosis. I'm too young. I'm asking God, "Why me? I already have MG, and now this. Why is it so unfair? and Why am I still living?" I tried to act normal every time I'm having my regular check-up but deep inside, I felt like losing again. It's another battle and I don't know what to do, I haven't told anyone in my family because I don't want to bother them. The have already sacrificed a lot when I was in MG crisis. The cost of my medications for MG and POI are a lot but I was able to manage through my Persons with Disability Card and enrolment in DSWD. Even though I have a boyfriend now, I have decided not to plan on having my own family because I want to focus on my recovery.

So how do I cope in this situation? I don't look too much on the problem. As long as I am not experiencing MG crisis, that is fine. I keep on praying and believing that the Lord has plans. He already did a miracle before, I know He can do more for me. This disease is not easy and ordinary but with the help of people around me, I realized that I am living for them and with them. Through following the medications properly and having regular check-up, I believe that I can overcome this. Nobody knows what the future might be but we know Who holds the future.

References

1. Desai MK, Brinton RD. Autoimmune disease in women: Endocrine transition and risk across the lifespan. Front Endocrinol (Lausanne) 2019;10(APR).
2. Cao L, Liu W, Zhu Z. Clinical characteristics and relationship between myasthenia gravis and premature ovarian failure:report of two cases. J Int Med Res 2019; 47(8): 3992–7.
3. Liu X, Li R, Jinh Y. Resolution of primary ovarian insufficiency after corticosteroid administration in a myasthenia gravis patient: Report and minireview of literature. Neurol India 2018; 66: 1807-10.
4. European Society of Human Reproduction and Endocrinology. Management of women with premature ovarian insufficiency: Guideline of the European Society of Human Reproduction and Embryology. 2015;(December).
5. Nguyen HH, Milat F & Vincent A. Premature ovarian insufficiency in general practice: Meeting the needs of women. Australian Family Physician 2017; 46(6): 360–6.
6. Dragojevic-Dikic S, Marisavljevic D, Mitrovic A, Dikic S, Jovanovic T, Jankovic Raznatovic S. An immunological insight into premature ovarian failure (POF). Autoimmun Rev 2010; 9(11):771–4.
7. Çakır ED, Özdemir Ö, Eren E, Saglam H, Okan M, Tarım ÖF. Resolution of autoimmune oophoritis after thymectomy in a myasthenia gravis patient. J Clin Res Pediatr Endocrinol 2011; 3(4): 212-5.
8. Delpy L, Douin-Echinard V, Garidou L, Bruand C, Saoudi A, Guéry JC. Estrogen enhances susceptibility to experimental autoimmune myasthenia gravis by promoting type 1 polarized immune responses. J Immunol October 15, 2005, 175 (8): 5050-7.
9. Li Y, Xiao B, Xiao L, et al. Myasthenia gravis accompanied by premature ovarian failure and aggravation by estrogen. Intern Med 2010.
10. Kuki S, Morgan RL, Tucci JR. Myasthenia gravis and premature ovarian failure. Arch Intern Med 1981; 141(9):1230–2.
11. Chung TK, Haines CJ and Yip SK. Case report: spontaneous pregnancy following thymectomy for myasthenia gravis associated with premature ovarian failure. Asia Oceania J Obstet Gynaecol 1993; 19: 253–5.

12. Ryan MM, Jones HR Jr. Myasthenia gravis and premature ovarian failure. Muscle Nerve 2004 Aug; 30(2):231-3.
13. Dong, JD, Wang, XS, Jin, L. Myasthenia gravis complicated with premature ovarian failure 1 cases report. J Clin Neurol 2011; 24: 117.
14. Nancy P, Berrih-Aknin S. Differential estrogen receptor expression in autoimmune myasthenia gravis. Endocrinology 2005; 146(5): 2345–53.
15. Sullivan SD, Sarrel PM, Nelson LM. Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. Fertil Steril 2016; 106(7):1588–99.
16. Cao L, Liu W, Zhu Z. Clinical characteristics and relationship between myasthenia gravis and premature ovarian failure: report of two cases. J Int Med Res 2019; 47(8): 3992–7.
17. Chae-Kim JJ, Gavrilova-Jordan L. Premature ovarian insufficiency: procreative management and preventive strategies. Biomedicines 2018;7(1): 2. doi:10.3390/biomedicines7010002.
18. Stimpfel M, Skutella T, Cvjeticanin B, et al. Isolation, characterization and differentiation of cells expressing pluripotent/multipotent markers from adult human ovaries. Cell Tissue Res 2013; 354: 593-607.