Background

Myasthenia gravis (MG) is an acquired chronic autoimmune disorder. It is caused by autoantibodies that block the muscle nicotinic acetylcholine receptor (AChR) on the postsynaptic membrane of the neuromuscular junction, leading to a deficit of AChR at the neuromuscular junction, which results in insufficient nerve-impulse transmission to striated muscles [1]. The symptoms of MG are characterized by varying degrees of weakness and easy fatiguability of striated muscles [1]. The worldwide incidence rate of MG is between 1 in 10,000 and 1 in 50,000, and MG is twice as common in women as in men [2-4]. The onset age of MG is commonly within the second and third decades of life, which overlaps with childbearing years in women. Estimations of prevalence of MG in pregnancy vary greatly due to regional discrepancies. The incidence of MG in pregnancy reported by western countries is approximately 1 in 20,000 [2-4], while recent studies from Taiwan and China show an incidence of 7 in 20,000 and 5 in 20,000 in these two regions respectively [5, 6].

The clinical course of MG during pregnancy is highly variable and unpredictable. Most reports describe that approximately one third of women experience an exacerbation of their MG during pregnancy [7 -9], but some studies show significantly higher or lower rates of exacerbation [3, 10, 11]. Exacerbation of MG can occur at all stages of pregnancy and the postpartum period [7 -11]. Severe MG deterioration may lead to myasthenic crisis, which substantially increases mortality risk in both the fetus and the mother. Literature on the effects of MG in pregnancy is contradictory. Hoff et al. have reported that MG increases the risk of complications during delivery [12]. In contrast, recent studies suggest that MG does not have adverse effects on pregnancy and delivery [5, 13, 14]. Since anti acetylcholine-receptor (anti-AchR) antibodies are able to cross through the placenta, the fetus is likely to be affected as well. The reported incidence of transient neonatal MG varies between 9% and 30% [3,11]. The purpose of this study was to review the clinical course of MG in 8 Chinese pregnant women and evaluate the effects of MG on pregnancy, delivery, and neonatal outcome.
2 Case presentation

2.1 Status and management of MG before pregnancy

Eight pregnant women with MG were treated and gave birth at the Department of Gynecology and Obstetrics of our hospital between 2004 and 2012. The patients were diagnosed with MG at the hospital’s Department of Neurology. The patients underwent regular examinations during pregnancy and postpartum period by both obstetricians and neurologists in our hospital.

The mean age of the patients was 27.5 years (21-31 years). All the patients were primigravida. The mean prior duration of MG was 8.1 years (3-18 years). Prior to pregnancy, one patient was in remission, six patients had stable MG, and one had unstable MG and had been recommended to postpone pregnancy. The patients were treated with common therapies for MG including thymectomy, immunosuppressant drugs and oral anticholinesterase agents. Five patients underwent thymectomy before pregnancy. Two patients were taking oral pyridostigmine 120-180 mg/d alone. The remission patient had been treated with oral pyridostigmine 60-300 mg/d when she was diagnosed with MG, and became stable after 3 months of medication. She stopped the medication voluntarily one year after the onset of MG and remained asymptomatic before pregnancy. The status and management of MG prior to pregnancy of the 8 patients is illustrated in Table 1.

Informed consent: Informed consent has been obtained from all individuals included in this study

| Patient ID | Age (years) | Duration of MG (years) | Thymectomy | Medication (dosage) | MG Status |
|------------|-------------|------------------------|-------------|---------------------|-----------|
| 1          | 27          | 3                      | Yes         | Prednisone (10 mg/d)| Stable    |
| 2          | 27          | 5                      | Yes         | Prednisone (10 mg/d)| Stable    |
| 3*         | 31          | 10                     | Yes         | Prednisone (30 mg/d)| Stable    |
| 4          | 21          | 18                     | No          | Pyridostigmine (180 mg/d)| Stable    |
| 5*         | 28          | 13                     | Yes         | Prednisone (40 mg/d) + pyridostigmine (30 mg/d) | Unstable |
| 6          | 28          | 10                     | Yes         | Prednisone (30 mg/d) + pyridostigmine (240 mg/d) | Stable    |
| 7*         | 27          | 10                     | No          | None                | Remission |
| 8          | 31          | 10                     | No          | Pyridostigmine (120 mg/d) | Stable    |

* indicated the patients with MG exacerbation during pregnancy or puerperium.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the Institutional Ethics Committee of the First Affiliated Hospital of Wenzhou Medical College.

2.2 Clinical course of MG during pregnancy and puerperium

In five of the patients, MG remained stable during pregnancy. The contribution of medication to stabilize MG in pregnancy seems inconclusive. Discontinuation of low dosage medication for MG (patient #2 and #8) or small reduction (patient #6) of prednisone or anticholinesterase inhibitors did not appear to adversely affect the course of MG during pregnancy. However, patient #3, who reduced the dosage of prednisone at the beginning of pregnancy, developed exacerbation of MG at the 24th week of pregnancy. The anticholinesterase inhibitor, pyridostigmine, was added to keep her MG in control during the remaining period of pregnancy. She became critically ill six days after caesarean section due to lung infection and MG deterioration, and was transferred to intensive care unit and treated with prednisone at 60 mg/d plus pyridostigmine at 240 mg/d accompanied by intravenous injection of immunoglobulin at 175 g/d for 5 days. She recovered gradually and her MG remained stable thereafter.

Patient #7 had remitting MG prior to pregnancy, and remained stable, free of medication, during the pregnancy. However, she experienced MG deterioration one month after delivery. She was then treated with oral
pyridostigmine at 60 mg/d and the dosage was reduced to 30 mg/d after her MG condition became stable.

Patient #5 had unstable MG prior to pregnancy and conceived accidentally. This patient voluntarily discontinued her medication for MG at the 6th week of pregnancy. Her MG deteriorated at the 30th week of pregnancy and she gave birth prematurely at 34th week of pregnancy. Her baby exhibited transient neonatal myasthenia gravis (NMG). Both the mother and the infant were promptly treated and recovered well. The summary of the clinical course of MG of all the patients is presented in Table 2.

### 2.3 The effects of MG on pregnancy, delivery, and neonatal outcome

Excepting patient #5 who had preterm labor due to exacerbation of MG, the other 7 patients had uneventful full-term pregnancies. Three patients delivered by caesarean section. Patient #5 had caesarean section due to exacerbation of MG associated with preterm labor. Caesarean section was performed on patient #3 and #4 for obstetric reasons. Although patient #3 had MG deterioration at the 24th week of pregnancy, she had a full-term pregnancy and gave birth to a healthy infant. Neonatal MG (NMG) was seen only in the premature baby whose mother had unstable MG prior to pregnancy and who experienced exacerbation of MG exasperation during pregnancy, while the other 7 infants were healthy. The average birth weight of the infants whose mothers experienced MG deterioration was $2717 \pm 89$ g, which is lower than those whose mothers with stable MG status ($3310 \pm 227$ g), suggesting that women who experience exacerbation of MG during pregnancy tend to give birth to infants with lower birth weight. The data were summarized in Table 3.

| Patient ID | Medication during pregnancy (dosage) | MG Status |
|------------|------------------------------------|-----------|
| 1          | Prednisone (10 mg/d)                | Stable    |
| 2          | Prednisone was discontinued at the beginning of pregnancy. | Stable |
| 3*         | Prednisone was reduced from 30 mg/d to 10 mg/d. Pyridostigmine (60 mg/d) was added at the 24th week of pregnancy. | Deteriorated at the 24th week of pregnancy. The patient was critically ill 6 days after the caesarean section due to lung infection and MG exacerbation. |
| 4          | Pyridostigmine (180 mg/d)           | Stable    |
| 5*         | Both prednisone and pyridostigmine were discontinued voluntarily at the 6th week of pregnancy | Deteriorated at the 30th week of pregnancy. |
| 6          | The dosage of prednisone and pyridostigmine was reduced from 30 mg/d and 240 mg/d to 20 mg/d and 120 mg/d, respectively. | Stable |
| 7*         | None                                | Deteriorated at puerperium |
| 8          | Pyridostigmine was discontinued     | Stable    |

* indicated the patients with MG exacerbation during pregnancy or puerperium.

| Patient ID | Gestation period (weeks + days) | Complications in pregnancy | Delivery | Infant body weight (g) | Infant outcomes |
|------------|---------------------------------|-----------------------------|----------|------------------------|-----------------|
| 1          | 39+2                            | None                        | Vaginal  | 3900                   | Good            |
| 2          | 38+4                            | None                        | Vaginal  | 3450                   | Good            |
| 3*         | 37+4                            | None                        | Caesarean section | 2860               | Good            |
| 4          | 40+4                            | None                        | Caesarean section | 3400               | Good            |
| 5*         | 34                              | Preterm delivery            | Caesarean section | 2490               | NMG             |
| 6          | 40                              | None                        | Vaginal  | 2500                   | Good            |
| 7*         | 39+2                            | None                        | Vaginal  | 2800                   | Good            |
| 8          | 38+6                            | None                        | Vaginal  | 3300                   | Good            |

* indicated the patients with MG exacerbation during pregnancy or puerperium.
2.4 Patient follow-up

All the mothers and their babies came back to follow-up visit regularly. MG condition of all the mothers is stable now and all the babies are healthy.

3 Discussion

3.1 Clinical course of MG during pregnancy and puerperium

The clinical course of MG during pregnancy is highly variable and unpredictable. Consistent with the most reported deterioration rate of MG during pregnancy [7-9], we observed 37.5% (3/8) of patients experienced exacerbation of MG during pregnancy. It is thought that MG exacerbation usually occurs during the first trimester and puerperium, while improvement of symptoms likely occurs during the second and third trimester due to normal immunosuppressive changes in late pregnancy [15]. However, we found that MG exacerbation occurred in the second, third, and puerperium in our patients, further supporting the high variation in MG during pregnancy.

Prediction of MG exacerbation during pregnancy is challenging. The clinical state of MG before pregnancy usually is not of value in predicting the exacerbation or remission of the disease during pregnancy. For example, patient #3 in our study, who had MG for 10 years and was stable prior to pregnancy, experienced deterioration at the 24th week of pregnancy. Patient #7 who had remitting MG prior to pregnancy developed MG exacerbation during puerperium, although her MG remained stable during pregnancy. Thus, stable or remitting MG before pregnancy does not appear to reduce the possibility of exacerbation during pregnancy or puerperium. Interestingly, our study suggests that women who have unstable MG before pregnancy and who discontinue medication for MG during pregnancy could be at higher risk of severe MG deterioration. In our study, patient #5 who had unstable MG prior to pregnancy not only failed to follow the recommendation to postpone pregnancy, but also voluntarily discontinued the medication for MG. Her MG deteriorated in the third trimester, leading to preterm delivery of an NMG infant. Hence, it appears that patients with unstable MG should delay pregnancy to avoid the risk of severe MG exacerbation.

In addition, it has been suggested that high risk of mortality during pregnancy is associated with shorter prior duration of MG, while women with longer than 7 years from onset of MG tend to have a lower risk of mortality during pregnancy [16]. Djelmis et al. also demonstrated that women who experience exacerbations during the puerperium have significantly shorter prior duration of MG than those who do not [8]. However, in our study, all the patients who developed exacerbation during pregnancy or puerperium had a history of MG longer than 10 years, and the patients who had short duration of MG (patient #1 and #2) remained stable during pregnancy and puerperium. Although the number of patients in our study is too small for any statistical analysis, we believe that the length of MG duration might not be a good predictor of the course of disease during pregnancy or puerperium.

The standard therapies for MG include thymectomy and pharmacological interventions such as immunosuppressant and acetylcholine esterase inhibitors. Reports about the effects of thymectomy on the course of MG during pregnancy show inconsistent conclusions. Roth et al. have found that women who undergo thymectomy prior to pregnancy have a better course of MG during pregnancy and postpartum period than those who do not [17]. On the contrary, Hoff et al. reported that thymectomy prior to pregnancy did not affect the clinical course of MG during pregnancy, but significantly reduces the risk of NMG [18]. In our study, the rate of exacerbation (33%, 1/3) among the patients who did not undergo thymectomy prior to pregnancy was similar to those who did (40%, 2/5), suggesting that thymectomy prior to pregnancy might not decrease the risk of exacerbation during pregnancy and puerperium.

Data on the safety of pharmacological treatment for MG during pregnancy are still lacking. Corticosteroid drugs such as prednisolone and prednisone are thought to present little teratogenic risk to the fetus [19], and only a slight increase in incidence of cleft palate has been reported (<1%) [20]. Pyridostigmine, which is an acetylcholine esterase inhibitor, is generally considered safe during pregnancy when used at the appropriate dosage [14, 21]. Only one case of microcephaly due to high dose of pyridostigmine use in the mother has been reported [22]. In our study, some patients (patient #1 and #4) needed continue on prednisone or pyridostigmine during pregnancy, and in other patients either the medication was discontinued (patient #2, #5, and #8) or the dosage of medication was reduced (patient #3 and #6). Regardless of the medication regimens during pregnancy, all infants born to our patients exhibited no congenital abnormalities. Our finding indicates that prednisone (10-20 mg/d) and pyridostigmine (60-180 mg/d) may be safe for both mother and fetus when used appropriately.

We believed that sudden withdrawal of relatively high dosage of immunosuppressive medication during
pregnancy should be avoided for women with MG, particularly for women with unstable MG prior to pregnancy, which could cause severe exacerbation due to the restoration of immunological reaction to AchR. Our study presented a case of unstable MG prior to pregnancy (patient #5) with a sudden withdrawal of prednisone (40 mg/d) and pyridostigmine (30 mg/d) at the beginning of pregnancy. She experienced MG deterioration in the third trimester, resulting in preterm delivery of a NMG infant. Based on this case, we suspect that the exacerbation might be associated with the sudden withdrawal of corticosteroid medication during pregnancy. Nevertheless, we do recommend adjusting the dosage and dose interval throughout the pregnancy since the ongoing physiological changes during pregnancy may inhibit the absorption of any oral medication. The dosage of medication of MG during puerperium should be restored to the dosage that effectively stabilizes the MG before pregnancy.

Plasma exchange and intravenous immunoglobulin are used as short-term treatments for impending and manifest myasthenic crisis and in patients with significant respiratory or bulbar dysfunction [23]. With MG patients during pregnancy, both plasma exchange and intravenous immunoglobulin therapies have been proven to be effective, safe and well tolerated [24]. In the current study, patient #3 recovered with prednisone, pyridostigmine and immunoglobulin.

3.2 The effects of MG on pregnancy, delivery, and neonatal outcome

We found that 88% (7/8) of our patients had uneventful full-term pregnancy, suggesting that MG might not adversely affect pregnancy even if MG exacerbation occurs. The rate of NMG in our study was 12.5% (1/8), which is within the range (9%– 30%) reported by others [3, 11]. Although it has been demonstrated that the severity of maternal MG and the antibody titer of the mothers do not correlate with the occurrence of NMG [25], in our study the only NMG infant was born to the mother who had unstable MG prior to pregnancy and experienced MG exacerbation in the third trimester, suggesting that women with unstable MG might pose increased NMG risk to the fetus if they become pregnant. In addition, Wen et al. have found that there is no significant difference in the risk of having infants with low birth weight between women with and without MG [5]. Similarly, our study shows that the average birth weight of the infants in our study (3088 ± 178 g) is fairly close to the average birth weight of Chinese infants (3230 g) born to healthy mothers. However, we found that women with MG exacerbation during pregnancy appeared to have infants with lower birth weight than those who without MG exacerbation during pregnancy. Thus, for the benefit of the fetus, we recommend that women with MG should have their MG under control during pregnancy.

In summary, the course of MG during pregnancy is highly variable and unpredictable, thus, decisions should be very caution in the treatment of women with MG contemplating pregnancy or with presentation during pregnancy. The status of MG during pregnancy should be monitored closely. The management of MG during pregnancy should not be altered abruptly. We strongly recommend that women with unstable MG postpone pregnancy to avoid potential severe MG deterioration and adverse effects on the fetus.

Acknowledgment: This work was supported by Science and Technology Development Funds of Wenzhou city (Y20170582 and Y20170118)

Conflict of interests: Authors state no conflict of interests.

References

[1] Drachman DB. Myasthenia gravis. N Engl J Med. 1994, 330:1797-810.
[2] Plauché WC. Myasthenia gravis. Clin Obstet Gynecol. 1983, 26:592-604.
[3] Mitchell PJ, Bebbington M. Myasthenia gravis in pregnancy. Obstet Gynecol. 1992,80:178–181.
[4] Kalidindi M, Ganpot S, Tahmesebi F, Govind A, Okolo S, Yoong W. Myasthenia gravis and pregnancy. J Obstet Gynaecol. 2007, 27:30-32.
[5] Wen JC, Liu TC, Chen YH, Chen SF, Lin HC, Tsai WC. No increased risk of adverse pregnancy outcomes for women with myasthenia gravis: a nationwide population-based study. Eur J Neurol. 2009, 16:889-894.
[6] Qi QW, Wang D, Liu JT, Bian XM. Management of pregnancy with myasthenia gravis: 7 cases report. Zhonghua Fu Chan Ke Za Zhi. 2012, 47:241-244.
[7] Schlezinger NS. Pregnancy in myasthenia gravis and neonatal myasthenia gravis. Am J Med. 1955, 19:718-20.
[8] Djelims J, Sostarko M, Mayer D, Ivanisic M. Myasthenia gravis in pregnancy: report on 69 cases. Eur J Obstet Gynecol Reprod Biol. 2002, 104: 21-25.
[9] Tellez-Zenteno JF, Hernandez-Ronquillo L, Salinas V, Estanol B, da Silva O. Myasthenia gravis and pregnancy: clinical implications and neonatal outcome. BMC Musculoskelet Disord. 2004, 5:42-47.
[10] Picone O, Audibert F, Gajdos P, Fernandez H. Myasthenia gravis and pregnancy: report of 13 cases. J Gynecol Obstet Biol Reprod (Paris). 2003, 32: 654-659.
[11] Batocchi AP, Majolini L, Evoli A, Lino MM, Minisci C, Tonali P. Course and treatment of myasthenia gravis during pregnancy. Neurology. 1999, 52: 447-452.

[12] Hoff JM, Daltveit AK, Gilhus NE. Myasthenia gravis consequences for pregnancy, delivery and the newborn. Neurology. 2003, 61: 1362-1366.

[13] Ferrero S, Esposito F, Biamonti M, et al. Myasthenia gravis during pregnancy. Expert Rev Neurother. 2008, 8: 979-988.

[14] Chaudhry SA, Vignarajah B, Koren G. Myasthenia gravis during pregnancy. Can Fam Physician. 2012, 58:1346-1349.

[15] Ferrero S, Pretta S, Nicoletti A, Petrera P, Ragni N. Myasthenia gravis: management issues during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2005, 121: 129–138.

[16] Scott JS. Immunologic diseases in pregnancy. Prog Allergy. 1977, 23:371–375.

[17] Roth TC, Raths J, Carboni G, Rosler K, Schmid RA. Effect of pregnancy and birth on the course of myasthenia gravis before or after transsternal radical thymectomy. Eur J Cardiothorac Surg. 2006, 29:231-235.

[18] Hoff JM, Daltveit AK, Gilhus NE. Myasthenia gravis in pregnancy and birth: identifying risk factors, optimising care. Eur J Neurol. 2007, 14:38-43.

[19] Martinez-Rueda JO, Arce-Salinas CA, Kraus A, et al. Factors associated with fetal losses in severe systemic lupus erythematosus. Lupus. 1996, 5:113–119.

[20] Rodriguez-Pinilla E, Martinez-Frias ML. Corticosteroid during pregnancy and oral clefts: a case-control study. Teratology. 1998, 58:2–5.

[21] Ciafaloni E, Massey JM. The management of myasthenia gravis in pregnancy. Semin Neurol. 2004, 24:95-100.

[22] Dominovic-Kovacevic A, Ilic T, Vukojevic Z. Myasthenia gravis and pregnancy case report. Curr Top Neurol Psychiatr Relat Discip. 2010, 18:40-43.

[23] Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, Kuntz N et al. International consensus guidance for management of myasthenia gravis: Executive summary. Neurology. 2016, 87(4):419-25.

[24] Hassan A, Yasawy ZM: Myasthaenia Gravis. Clinical management issues before, during and after pregnancy. Sultan Qaboos Univ Med J. 2017, 17(3):e259-e267.

[25] Saint-Faust M, Perelman S, Dupont D, Velin P, Chatel M. Transient neonatal myasthenia gravis revealing a myasthenia gravis and a systemic lupus erythematosus in the mother: case report and review of the literature. Am J Perinatol. 2010, 27:107-110.