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RESEARCH PAPER

Myasthenia in pregnancy: best practice guidelines from a UK multispecialty working group

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ABSTRACT

A national UK workshop to discuss practical clinical management issues related to pregnancy in women with myasthenia gravis was held in May 2011. The purpose was to develop recommendations to guide general neurologists and obstetricians and facilitate best practice before, during and after pregnancy. The main conclusions were (1) planning should be instituted well in advance of any potential pregnancy to allow time for myasthenic status and drug optimisation; (2) multidisciplinary liaison through the involvement of relevant specialists should occur throughout pregnancy, during delivery and in the neonatal period; (3) provided that their myasthenia is under good control before pregnancy, the majority of women can be reassured that it will remain stable throughout pregnancy and the postpartum months; (4) spontaneous vaginal delivery should be the aim and actively encouraged; (5) those with severe myasthenic weakness need careful, multidisciplinary management with prompt access to specialist advice and facilities; (6) newborn babies born to myasthenic mothers are at risk of transient myasthenic weakness, even if the mother's myasthenia is well-controlled, and should have rapid access to neonatal high-dependency support.

INTRODUCTION

Myasthenia gravis (MG), an autoimmune condition due to antibodies against the nicotinic acetylcholine receptor (AChR) or other postsynaptic antigens (eg, muscle specific kinase, MuSK), has an estimated population prevalence of between 126[1] and 400 per million.[2] Under the age of 40, generalised myasthenia is significantly more common in women.[3] Diagnosis is made through recognition of the cardinal clinical features of fatigable, painless muscle weakness with confirmatory serum autoantibody analysis and electromyographic evidence of disordered neuromuscular transmission, thereby excluding other differential diagnoses. Symptomatic improvement may be achieved through the use of anticholinesterase drugs, although usually immune-directed treatments are required to control the condition and induce remission.

Previous studies

A number of studies examining the course of myasthenia during and after pregnancy have been published since 1985 and are summarised in table 1.

Overall, the view of the workshop was that the existing literature was of limited value in extrapolating to current practice. Only one study was prospective. Many included historic patients not treated with what would now be regarded as standard immunosuppressive therapy. They varied widely in the depth of data and outcome measures provided; many were difficult to evaluate due to sparse detail, if any, provided on the neurological examination features and myasthenic status of the patients and little description of drug treatment during the pregnancy. There was broad agreement on certain points with marked differences on others. Myasthenia did not necessarily worsen during pregnancy, and indeed improved in many women, but several studies demonstrated a worsening during the puerperium. Many patients had a thymectomy before pregnancy. In several studies, drug treatment appeared minimal in many patients, which may suggest an atypical set of patients. The incidence of instrumental or caesarean deliveries was variable and particularly high in Taiwan.[10] There was a wide disparity in the figures for the occurrence of transient neonatal MG (TNMG), varying from 9%[5] to 30%,[6] although authors agreed that TNMG bore no relation to the mother's myasthenic disease status.

As myasthenia is uncommon, specific information regarding drug use in pregnancy is limited. However, safety data may be extrapolated from the use of immunosuppressant drugs in other autoimmune conditions and organ transplant recipients in pregnancy.

MATERIALS AND METHODS

Representatives of various disciplines were invited to attend the workshop by FN and CNP and were selected on the basis of current involvement in the care of myasthenic women or their children. The participants included paediatric and adult neuromuscular specialists, obstetricians, obstetric physicians, an obstetric anaesthetist, a Myasthenia Gravis Association nurse specialist and a patient. All participants were asked to contribute a talk and written text on their area of expertise. Discussion took place over 2 days via a structured programme. The recommendations document was drawn up by consensus at the end of the workshop with contributions from all present.

RESULTS AND DISCUSSION

Each topic area was discussed among the group and consensus reached as presented below.

Table 1 Summary of previously published studies of myasthenia in pregnancy

Lead author/ date	Number of patients in study	Drug treatment	Course during pregnancy	Course after delivery	Mode of delivery	Transient neonatal myasthenia gravis	Other comments
Plauché (1991)[4]	322 pregnancies in 225 women	Not stated	No change in 31.7% during pregnancy or puerperium, relapse in 41%, remission in 29%	29.8% exacerbation with 4% death rate	Pre-1963 CS 5.6%; post-1963 13.5%. 15.4% forceps.	16.1% (14.9% definite)	Large review series
Batocchi* (1999)[5]	64 pregnancies in 47 women	Majority on PYR, very few on immunosuppression (ST, AZA)	17% relapse in patients on no therapy; on therapy 39% improved, 19% relapsed, 42% unchanged. Combined groups 60% worse first trimester, 10% second, 30% third.	28% worse	CS rate 30%, most for obstetric reasons	9%	42 had thymectomy preconception: hyperplasia in 35, thymoma 4
Djelmis (2002)[6]	69 pregnancies in 65 women	23% no drug treatment, 43% PYR alone, 33% on ST as well. AZA stopped 6–12 months before conception if planned. Nine patients had plasma exchange.	14.5% worse, 22% unchanged, 25% improved.	16% worse	Vaginal in 83%, vacuum extraction in 9% and CS in 17% (all but one for obstetric reasons).	30%	38.5% had thymectomy prepregnancy
Hoff (2003)[7]	127 births in 79 women (1967–2000)	Not recorded prior to 1999, thereafter PYR alone in 54.5%.	Not stated	Not stated	Caesarean rate 17.3%, many elective. Forceps/ vacuum in 8.7%	5 babies had severe anomalies with TNMG in (a different) 5 (4%).	Data from Birth Registry. 35.4% prepregnancy thymectomy
Hoff (2004)[8]	49 births in 37 asymptomatic/in remission mothers	Not stated	Not stated	Not stated	Protracted labour. CS 14.6%, forceps/vacuum 8.2%	Increased perinatal mortality (6.1%)	
Hoff (2007)[9]	135 births in 73 mothers	Medication in 68% but in only 45% throughout pregnancy: PYR alone apart from one on ST and three crisis management	10% worse	Not stated	Protracted labour 19%	19%	Risk of TNMG halved if mother had had a thymectomy
Wen (2009)[10]	163 women	Not stated	Not stated	Not stated	CS 44.8% (but 37.4% for all births)	No significantly increased risk to baby.	Concluded that no significant risk of adverse pregnancy outcome
Almeida (2010)[11]	Anaesthetic management of 17 women	Not stated	4 worse, 8 no change, 3 first presentation	Not stated	CS in 5 (of 8 stable) women	None reported	

*Prospective study.
AZA, azathioprine; CS, caesarean section; PYR, pyridostigmine; ST, corticosteroids; TNMG, transient neonatal MG.

Myasthenia in adolescents and young women

Preparation for potential pregnancy should start well in advance. Opportunities for counselling occur at each outpatient visit to the neurologist, and the possibility of pregnancy should always be considered particularly when choosing immunosuppressant drugs. Optimisation of myasthenic status may be straightforward in principle, but in many patients may take months or longer to achieve. The myasthenia specialist nurse can be very helpful in supporting women and their partners and allowing time for concerns about pregnancy to be raised. They may also act as a link point for access to other services, monitoring symptoms in case of relapse and addressing anxieties.

Safety of drugs for myasthenia

A number of the drugs used to treat MG can safely be continued in pregnancy and during breast feeding. Women require confident reassurance about the safety profile of their drugs in pregnancy and also counselling regarding the likely detrimental effect on their MG if they reduce or discontinue medication. Issues regarding the individual therapies are discussed below and are summarised in table 2.

Pyridostigmine

Pyridostigmine is ionised at physiological pH and therefore not expected to cross the placenta in significant amounts. There have been no reports of fetal malformations.[12] Breastfed infants of mothers taking pyridostigmine ingest <0.1% of maternal dose, and the American Academy of Paediatrics considers pyridostigmine to be compatible with breast feeding.[12]

Corticosteroids

Maintenance steroids at the lowest possible dose are usually continued in pregnancy as they cause minimal adverse effects to mother or fetus.[12] Steroids have been used to treat asthma,

Table 2 Safety of drugs used for myasthenia in pregnancy and breast feeding

Drug	Adverse effects	Comments	Safe in pregnancy	Safe in breast feeding
Pyridostigmine	None reported	Use as normal—may need more frequent doses	Yes	Yes
Prednisolone	No convincing data for increased risk of cleft lip/palate Increased risk of GDM, hypertension, infections	Use as normal—lowest effective dose. Screen for GDM	Yes	Yes
Azathioprine	Leucopenia	Use as normal. Monitor WBC and LFTs	Yes	Yes
Ciclosporin/ Tacrolimus	Increased risk of GDM and hypertension with tacrolimus	Use as normal. Screen for GDM Monitor WBC, LFTs and creatinine	Yes	Yes
Mycophenolate Mofetil	Teratogenic; quoted risks up to 25%	Withdraw or switch to an alternative immunosuppressant drug prepregnancy. Do not stop abruptly if unplanned pregnancy	No	Unknown
Methotrexate	Teratogenic; quoted risks up to 15–20%	Stop prepregnancy if possible. Allow 3 months wash out prepregnancy. Don't stop abruptly if unplanned pregnancy but give 5 mg folic acid daily	No	No
Intravenous immunoglobulin	None reported		Yes	Yes

GDM, gestational diabetes; LFTs, liver function tests; WBC, white blood cell count.

arthritis, inflammatory bowel disease and recipients of solid organ transplants in pregnancy for many decades. Prednisolone is preferred as it is metabolised by the placenta and only 10% crosses into the fetal circulation at maternal doses <20 mg.[13] Exposure to corticosteroids in the first trimester has been shown in some retrospective studies to increase rates of cleft lip and palate;[14 15] however, this has not been substantiated in prospective case–control studies.[16 17] Corticosteroid use is associated with an increased risk of gestational diabetes mellitus (GDM), elevations in blood pressure, infections particularly urinary tract infections and preterm deliveries.[18] Because of the increased risk of GDM, screening with a glucose tolerance test is recommended at 28 weeks or sooner if there are other risk factors. Mothers receiving more than 7.5 mg prednisolone per day (or 15 mg on alternate days) for more than 2 weeks prior to delivery should receive parenteral steroids to cover the stress of delivery. Prolonged treatment is also associated with a risk of adrenal suppression, and a tetracosactrin test should be considered. Steroids can also be continued during breast feeding, and there is evidence that neonatal adrenal suppression following exposure *in utero* or during breast feeding does not occur.

Azathioprine

Azathioprine[19] is safe to use throughout pregnancy and breast feeding.[20] Azathioprine is a prodrug that is metabolised to 6-mercaptopurine (6MP). 6MP is converted intracellularly to active nucleotides (thioguanine nucleotides, TGN). The immature fetal liver does not express inosinate pyrophosphorylase, the enzyme that converts azathioprine to its active metabolites, and, therefore, is relatively protected from the clinical effects of the drug. Studies in women receiving thiopurines for renal disease, inflammatory bowel disease[21] and connective tissue disease do not demonstrate an increased risk of prematurity, congenital malformations or childhood neoplasia. If azathioprine is started during pregnancy, it is advisable to check the thiopurine methyltransferase activity to allow an appropriate dose to be used.

Mycophenolate mofetil (MMF)

Mycophenolate mofetil (MMF) is now a first-line agent for the treatment of lupus nephritis and transplantation. It is, however, a teratogen causing a typical clinical syndrome including hypoplastic nails, shortened fifth fingers, diaphragmatic hernia, microtia, micrognathia, cleft lip and palate and congenital heart defects.[19 22 23] This strongly weighs against using it as a first-line immunosuppressant in fertile women, and women are now advised to switch from MMF at least 3 months before conception to an immunosuppressive agent that has a safer profile in pregnancy, for example azathioprine, ciclosporin or tacrolimus. There are some situations where alternatives have been tried without success or with serious side effects and MMF is the only treatment able to achieve disease stability. The woman needs to be counselled carefully about the relative risks to the fetus if she remains on MMF during her pregnancy.

Calcineurin inhibitors

This class of drugs inhibits signalling pathways that regulate T cell activation. Neither ciclosporin[24 25] nor tacrolimus[26] are teratogenic. However, there is an increased risk of GDM and hypertension in women taking tacrolimus,[27] and therefore, screening with a glucose tolerance test is recommended at 28 weeks or sooner if there are other risk factors.

Methotrexate

Methotrexate is a folate inhibitor and is absolutely contraindicated in pregnancy and breast feeding. If used prepregnancy, it is recommended that a washout period of at least 3 months is allowed before conception.

Intravenous immunoglobulin and plasma exchange

Intravenous immunoglobulin (IVIG) has been used in pregnancy to treat immune thrombocytopenic purpura, immunodeficiency syndromes and other autoimmune diseases and is considered safe.[28 29] Plasma exchange may also be used if required and has been shown to be safe when used in pregnancy to treat thrombotic thrombocytopenic purpura[30] and haemolytic uraemic syndrome.

Antenatal care

Once pregnant, it is important to avoid factors that can cause an exacerbation of myasthenia such as initiation of certain drugs or withdrawal of immunosuppressant agents. Infections should be sought and treated promptly. Thyroid status should be checked at the booking visit if not before. A standard schedule of

antenatal care is appropriate but regular visits to a joint obstetric neurology clinic, where maternal and fetal well-being can be accessed by practitioners with expertise in the management of MG in pregnancy, is the ideal. Women should be encouraged to monitor fetal movements from 24 weeks' gestation, and if there is any concern regarding reduced fetal movements or abnormal assessments of uterine size, then ultrasound scanning to assess fetal growth, liquor volume and fetal movements should be performed (box 1). Guidance concerning drugs to be used with caution in women with MG should be incorporated into the hand-held pregnancy notes.

Preparation for delivery

The timing and place of delivery should be established through multidisciplinary discussion but should always be hospital-based and ideally with neurological and neonatal backup available and high-dependency care facilities. Spontaneous delivery at term should be the aim, provided that there is no deterioration in the mother's myasthenic control.

Obstetric anaesthesia

Any pregnant woman with MG should have a meeting with an obstetric anaesthetist prior to labour to discuss options for analgesia and/or anaesthesia for caesarean section. For the woman planning a spontaneous vaginal delivery, epidural or combined spinal-epidural anaesthesia may protect from prolonged overexertion and fatigue and can provide the necessary anaesthesia for an instrumental or caesarean delivery if required. Nitrous oxide (Entonox) can be used as normal in a patient with MG. Pethidine and other opioids should be avoided altogether as they may exacerbate respiratory depression in mother or fetus. Normal medications should be continued preoperatively, even in the elective setting.[31 32]

The main anaesthetic challenges in a patient with MG arise if regional anaesthesia is not possible and a general anaesthetic is required. Standard practice in obstetric anaesthesia is a rapid sequence induction of anaesthesia with thiopentone or propofol followed by a 'depolarising' muscle relaxant (suxamethonium) to facilitate tracheal intubation. Anaesthesia is then maintained with a volatile agent, opioids are used to achieve analgesia and further muscle relaxation drugs (usually non-depolarising relaxants) are administered as required. However, patients with MG are very sensitive to muscle relaxants, and the starting dose, if these drugs are required, should be substantially lowered. If at all possible, muscle relaxants should be avoided altogether in patients with MG. A peripheral nerve stimulator must be used to monitor the function of the neuromuscular junction in all patients who have received muscle relaxants.

Care of mother in postnatal period

Patients should be warned of the possibility of the need for postoperative ventilation on the intensive care unit, and they should be monitored closely by experienced recovery staff.

Care of the baby

Breast feeding should be encouraged, and the baby should receive all the usual recommended vaccinations.

Figures for the incidence of TNMG vary between 9% and 30% according to the literature as reviewed above. There is an agreement on the clinical features in the AChR-mediated syndrome, which comprise generalised hypotonia and weakness, ptosis, extraocular, bulbar and respiratory muscle involvement. Onset is not always immediate, may occur within hours or after a few days and persists from 2 weeks to several months. The

Box 1 Recommendations for management of myasthenia in pregnancy

- The consensus recommendations of the working group have been condensed into a two-sided A4 sheet with the intention of providing a ready-reference source for patients, general neurologists, obstetricians, midwives and paediatricians throughout the UK and for inclusion in the patient's hand-held maternity notes if applicable.

Prepregnancy

- Prepregnancy counselling should be opportunistic and offered to all female adolescents and women of childbearing age with MG in transitional and adult neurology clinics. If available, involve the MG specialist nurse in prepregnancy care.
- Ideally, pregnancy should be planned in women with MG. Every woman with MG should be seen by her neurologist before pregnancy and be given advice regarding optimal management of her MG. Specific advice about the safety of different therapies in pregnancy should be offered, with clear instructions not to discontinue safe immunosuppressive agents or pyridostigmine in pregnancy. In those known to be planning pregnancy in the near future, introduction of teratogenic drugs (methotrexate and MMF) should be avoided if possible. If they cannot be avoided, clear advice regarding the hazards and the need for effective contraception should be given.
- If required and appropriate, thymectomy should be performed before planned pregnancy.
- Thyroid antibody status and thyroid function tests should be determined prior to pregnancy so that women enter pregnancy euthyroid.

Pregnancy

- Women who have not received prepregnancy counselling should be offered the above advice in early pregnancy. Those who have unplanned pregnancies conceived while receiving methotrexate or MMF should be counselled about the possible adverse effects but abrupt withdrawal once pregnancy is confirmed may occur too late to avoid teratogenesis, risks deterioration in disease control and thus may not be appropriate. Women should again be reassured concerning the safety of prednisolone, azathioprine, ciclosporin and pyridostigmine in pregnancy and advised not to stop these drugs without advice.
- Women with MG should be managed during pregnancy by colleagues from different specialities working together, ideally a neurologist, specialist nurse/midwives, obstetrician with an interest in maternal medicine and obstetric anaesthetist. A care plan, including how to directly access advice from their neurological team, who should have expertise in the management of MG in pregnancy, should be drawn up and documented.
- Women with stable MG in pregnancy can be reassured that with current management most will not experience deterioration in their MG and that MG is unlikely to affect the timing or mode of delivery.
- Women with MG should have thyroid function tests performed early in pregnancy if they have not been performed within the year prior to pregnancy.
- As infection may precipitate deterioration in MG, and certain infections, particularly urinary tract infections, are more common in pregnancy, these should be sought and treated promptly with antibiotics appropriate for use in MG and in pregnancy.

- Guidance concerning drugs to be used with caution in women with MG should be incorporated into the hand-held pregnancy notes. Specific advice should be sought from pharmacy and the neurological team if a particular drug on the list is required since in many cases, particularly in women with stable disease control, this can be safely used with appropriate caution (http://www.myasthenia.org/whatismg/faqs.aspx).
- Pregnant women with MG should be referred to an obstetric anaesthetist, ideally before the late second/early third trimester of pregnancy.
- In pregnant women with MG, a fetal scan at 12 and 20 weeks' gestation should be offered. Encourage monitoring of fetal movements particularly after 24 weeks' gestation when these should be felt regularly. Perform 2–4 weekly antenatal examination to assess whether the uterine size is appropriate. If there are any concerns, arrange a fetal scan to assess for polyhydramnios and/or decreased fetal movements.
- Arthrogryposis in the fetus is a rare but recognised complication of maternal MG. If arthrogryposis is diagnosed in a current or previous pregnancy in a woman not known to have MG, investigations should include myasthenia antibodies and a search for myasthenic features in the mother because appropriate management will affect outcome.

Delivery

- There should be multidisciplinary team involvement in labour with obstetrician, anaesthetist and neonatologist, and neurological input should be accessible when required. On-site intensive care unit facilities should be available particularly for women with more severe disease.
- In women with well-controlled MG, vaginal delivery with spontaneous onset of labour should be the aim.
- Caesarean section should be performed only for obstetric indications. Women should continue their usual medications including oral anticholinesterases during labour. Women on long-term oral steroids (>7.5 mg per day or >15 mg on alternate days) should be given stress-dose parenteral hydrocortisone (100 mg tds IV) in labour.
- Many of the anaesthetic drugs deemed as 'contra-indicated' can be used safely in MG with appropriate monitoring. Even so, epidural analgesia is preferable to general anaesthesia whenever possible. Magnesium sulfate for eclampsia prophylaxis should be avoided. If a woman with MG has an eclamptic seizure, then magnesium sulfate should be given with extreme caution and in consultation with the obstetric anaesthetist and/or neurologist as intubation and ventilation may be required.
- Healthcare professionals and women with MG should be aware that TNMG is a recognised complication of maternal MG, regardless of the severity of the mother's disease. TNMG presents with hypotonia, muscle weakness, bulbar and respiratory involvement in the neonate. Therefore, delivery should occur in a unit with immediate neonatal/paediatric expertise and facilities for neonatal resuscitation. Delivery in midwifery-led units or home delivery is not appropriate.

Post partum

Mother

- Breast feeding should be encouraged and is not contraindicated with maternal prednisolone, azathioprine or pyridostigmine treatment.
- Be aware of possible deterioration in maternal MG in the postnatal period, particularly postsurgery and if any postpartum infection. Advise women to seek early review by their neurological team if they experience any deterioration in their symptoms.

Baby

- We recommend a period of postnatal observation for all infants of affected mothers, focusing on signs and symptoms indicative of TNMG, in particular bulbar and respiratory involvement. As onset of TNMG may be delayed for hours up to several days, at present we recommend an inpatient observation period of at least 2 days. As maternal MG secondary to MuSK antibodies may be associated with early and more severe neonatal manifestations, those infants warrant closer observation.
- Treatment of TNMG is mainly supportive through managing feeding difficulties and providing adequate respiratory support. In addition to cholinesterase inhibitors, IVIG ought to be considered in more severely affected infants. Exchange transfusions should be reserved for the most profoundly affected cases.
- Although TNMG by definition is a transient condition, a few children with maternal antibodies to the fetal AChR subunit may develop a persistent myopathy with associated velopharyngeal insufficiency.
- Neurophysiology is the most useful screening investigation in neonates/infants presenting with possible myasthenic symptoms in the absence of a maternal history and should be performed by an experienced clinician. This may be required when considering either neonatal myasthenia or a CMS.

more recently recognised form due to MuSK antibodies is thought to be more severe but less common.[33] Diagnosis of TNMG is through clinical examination of mother and child. Neurophysiology studies require great technical skill and are not available in the majority of centres. Antibody studies are not necessary as the mother's status will already be known, and the baby's antibody status will depend on the mother. Thus, if there is sufficient clinical evidence for TNMG, neonatal treatment should be initiated even if confirmatory evidence from laboratory tests is still awaited or unavailable. Treatment for milder cases is with supportive measures such as a nasogastric tube and assisted ventilation together with oral/nasogastric pyridostigmine or intramuscular/intravenous neostigmine. IVIG and possibly exchange transfusion may be required for severely affected infants, but this is exceptional.

Infants born to mothers with a high proportion of antibodies to the fetal γ-subunit of the AChR subunit may develop a severe and often fatal form of fetal arthrogryposis.[34 35] Milder cases may be viable but left with signs of a persistent myopathy, recently termed 'fetal AChR inactivation syndrome'[36] and attributed to inactivation of the fetal AChR receptor during a critical period of fetal development. Mothers with antibodies predominantly against the AChR γ-subunit may themselves be paucisymptomatic or asymptomatic, and the diagnosis of myasthenia in the mother is made only after recognising the fetal syndrome.

Paediatric myasthenia

Juvenile-onset autoimmune MG is rare, around 10% of the incidence of adult MG, but appears more common in Chinese children, with 50% of individuals with MG presenting in childhood, most (up to 75%) of whom remain ocular.[37] Confirmation of the

diagnosis is similar to that in adults with the same antibody pathophysiology, but seronegative cases are more common which should prompt testing for antibodies to clustered AChR and consideration of a congenital myasthenic syndrome (CMS) even if presentation is not from birth. Although, in contrast to adults, an underlying thymoma is exceedingly rare, it should nevertheless be excluded by appropriate imaging techniques as a few childhood cases have been reported. The spontaneous remission rate is higher than in adults, and the aim is to avoid aggressive treatment with immunosuppression, where possible, due to the long-term risks to growth and bone health and the rare possibility of late malignancy with azathioprine. Early thymectomy may be considered in those with AChR antibody-positive generalised disease who remain symptomatic despite optimal medical treatment.[38]

Congenital myasthenic syndromes

CMS are a heterogeneous group of rare conditions that present with myasthenic symptoms and signs at birth, in infancy or later. Typical presentations include ptosis, ophthalmoplegia, bulbar symptoms, stridor and occasionally respiratory crises. The syndrome arises through mutations in one of a number of genes responsible for the production of neuromuscular junction proteins, is not immune-driven and therefore does not respond to immunomodulation or suppression. Precise diagnosis and onward treatment is highly specialised and is best done in conjunction with a neuromuscular centre experienced in the diagnosis and management of these conditions. Occasionally, CMS can be unmasked during pregnancy or post partum and such an acute late presentation may be difficult to differentiate from autoimmune MG. Pregnant patients with CMS should be managed in the same way as autoimmune MG except they will not transfer antibodies to the fetus. In the absence of parental consanguinity, the risk of a mother with CMS giving birth to an affected child is very small because CMS are usually recessively transmitted (except for the slow channel syndrome which is autosomal dominant but usually presents later in childhood).

Patient perspective

In the United Kingdom, patients now have the option of support from the national network of myasthenia specialist nurses. Aspects that are offered include preconception advice and information, liaison with maternity services, advice about managing fatigue and weakness in pregnancy, facilitation of early assessment and symptom advice post partum and liaison with the health visitor and general practitioner.

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REFERENCES

1 Heldal AT, Owe JF, Gilhus NE, *et al*. Seropositive myasthenia gravis: a nationwide epidemiologic study. *Neurology* 2009;73:150–1.
2 MacDonald BK, Cockerell OC, Sander JW, *et al*. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 2000;123:665–76.
3 Grob D, Brunner N, Namba T, *et al*. Lifetime course of myasthenia gravis. *Muscle Nerve* 2008;37:141–9.
4 Plauché WC. Myasthenia gravis in mothers and their newborns. *Clin Obstet Gynecol* 1991;34:82–99.
5 Batocchi AP, Majolini L, Evoli A, *et al*. Course and treatment of myasthenia gravis during pregnancy. *Neurology* 1999;52:447–52.
6 Djelmis J, Sostarko M, Mayer D, *et al*. Myasthenia gravis in pregnancy: report on 69 cases. *Eur J Obstet Gynecol Reprod Biol* 2002;104:21–5.
7 Hoff JM, Daltveit AK, Gilhus NE. Myasthenia gravis: consequences for pregnancy, delivery, and the newborn. *Neurology* 2003;61:1362–6.
8 Hoff JM, Daltveit AK, Gilhus NE. Asymptomatic myasthenia gravis influences pregnancy and birth. *Eur J Neurol* 2004;11:559–62.
9 Hoff JM, Daltveit AK, Gilhus NE. Myasthenia gravis in pregnancy and birth: identifying risk factors, optimising care. *Eur J Neurol* 2007;14:38–43.
10 Wen JC, Liu TC, Chen YH, *et al*. No increased risk of adverse pregnancy outcomes for women with myasthenia gravis: a nationwide population-based study. *Eur J Neurol* 2009;16:889–94.
11 Almeida C, Coutinho E, Moreira D, *et al*. Myasthenia gravis and pregnancy: anaesthetic management—a series of cases. *Eur J Anaesthesiol* 2010;27:985–90.
12 Briggs GG, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation*. 9th edn. Lippincott: Williams and Wilkins, 2011.
13 Benediktsson R, Calder AA, Edwards CR, *et al*. Placental 11 beta-hydroxysteroid dehydrogenase: a key regulator of fetal glucocorticoid exposure. *Clin Endocrinol (Oxf)* 1997;46:161–6.
14 Park-Wyllie L, Mazzotta P, Pastuszak A, *et al*. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology* 2000;62:385–92.
15 Carmichael SL, Shaw GM, Ma C, *et al*. Maternal corticosteroid use and orofacial clefts. *Am J Obstet Gynecol* 2007;197:585.
16 Kallen B. Maternal drug use and infant cleft lip/palate with special reference to corticoids. *Cleft Palate Craniofac J* 2003;40:624–8.
17 Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. *Teratology* 1997;56:335–40.
18 Laskin CA, Bombardier C, Hannah ME, *et al*. Prednisone and aspirin in women with autoantibodies and unexplained recurrent fetal loss. *N Engl J Med* 1997;337:148–53.
19 Ostensen M, Brucato A, Carp H, *et al*. Pregnancy and reproduction in autoimmune rheumatic diseases. *Rheumatology (Oxford)* 2011;50:657–64.
20 Sau A, Clarke S, Bass J, *et al*. Azathioprine and breastfeeding: is it safe? *BJOG* 2007;114:498–501.
21 Francella A, Dyan A, Bodian C, *et al*. The safety of 6-mercaptopurine for childbearing patients with inflammatory bowel disease: a retrospective cohort study. *Gastroenterology* 2003;124:9–17.
22 Sifontis NM, Coscia LA, Constantinescu S, *et al*. Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. *Transplantation* 2006;82:1698–702.
23 Perez-Aytes A, Ledo A, Boso V, *et al*. In utero exposure to mycophenolate mofetil: a characteristic phenotype? *Am J Med Genet A* 2008;146A:1–7.
24 Bar Oz B, Hackman R, Einarson T, *et al*. Pregnancy outcome after cyclosporine therapy during pregnancy: a meta-analysis. *Transplantation* 2001;71:1051–5.
25 Armenti VT, Ahlswede KM, Ahlswede BA, *et al*. National transplantation Pregnancy Registry—outcomes of 154 pregnancies in cyclosporine-treated female kidney transplant recipients. *Transplantation* 1994;57:502–6.
26 Kainz A, Harabacz I, Cowlrick IS, *et al*. Review of the course and outcome of 100 pregnancies in 84 women treated with tacrolimus. *Transplantation* 2000;70:1718–21.
27 Armenti VT, Radomski JS, Moritz MJ, *et al*. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. *Clin Transpl* 2004;103–14.
28 Ateka-Barrutia O, Nelson-Piercy C. Management of rheumatologic diseases in pregnancy. Disclosures. *Int J Clin Rheumatol* 2012;7:541–58.
29 Friedman DM, Llanos C, Izmirly PM, *et al*. Evaluation of fetuses in a study of intravenous immunoglobulin as preventive therapy for congenital heart block: Results of a multicenter, prospective, open-label clinical trial. *Arthritis Rheum* 2010;62:1138–46.
30 Ganesan C, Maynard SE. Acute kidney injury in pregnancy: the thrombotic microangiopathies. *J Nephrol* 2011;24:554–63.
31 Banerjee A, Wilson I. Anaesthesia and Myasthenia Gravis. Anaesthesia Tutorial of the Week, World Federation of Societies of Anaesthesiologists. 2008. http://totw.anaesthesiologists.org/2008/12/14/anaesthesia-and-myasthenia-gravis-122/ (accessed online: 10/05/2011).
32 Gambling D, Douglas M, McKay R. *Obstetric anaesthesia and uncommon disorders*. UK: Cambridge University Press, 2008.
33 Niks EH, Verrips A, Semmekrot BA, *et al*. A transient neonatal myasthenic syndrome with anti-musk antibodies. *Neurology* 2008;70:1215–16.
34 Vincent A, Newland C, Brueton L, *et al*. Arthrogryposis multiplex congenita with maternal autoantibodies specific for a fetal antigen. *Lancet* 1995;346:24–5.
35 Oskoui M, Jacobson L, Chung WK, *et al*. Fetal acetylcholine receptor inactivation syndrome and maternal myasthenia gravis. *Neurology* 2008;71:2010–12.
36 D'Amico A, Bertini E, Bianco F, *et al*. Fetal acetylcholine receptor inactivation syndrome and maternal myasthenia gravis: a case report. *Neuromuscul Disord* 2012;22:546–8.
37 Zhang X, Yang M, Xu J, *et al*. Clinical and serological study of myasthenia gravis in HuBei Province, China. *J Neurol Neurosurg Psychiatry* 2007;78:386–90.
38 Chiang LM, Darras BT, Kang PB. Juvenile myasthenia gravis. *Muscle Nerve* 2009;39:423–31.

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