Thieme

Myasthenia Gravis: Family Planning, Pregnancy and Delivery

Authors
Andrea Thieme[1], Petra Kalischewski[2]

Affiliations
1 Helios Klinikum Erfurt, Neurologie, Erfurt
2 Neuropraxis Leipzig

Key words
pregnancy, delivery, Myasthenia gravis

Bibliography
DOI https://doi.org/10.1055/s-0043-122651
Neurology International Open 2018; 2: E46–E50

ISSN 2511-1795

Korrespondenzadresse
Dr. med. Andrea Thieme
Helios Klinikum Erfurt, Klinik für Neurologie
Zertifiziertes Integriertes Myasthenie Zentrum
Nordhäuser Str. 74
99089 Erfurt, Germany
andrea-thieme@helios-kliniken.de

ABSTRACT

Myasthenia gravis affects women younger than 40 about three times more frequently than men. Therefore, questions about family planning, pregnancy and delivery are common for these patients and their treating physicians. The outcome for mother and child depends a good deal on knowledge of the influence of pregnancy on myasthenia, therapy options, the relationship between the disease and delivery and the newborn. This paper provides an overview of these situations to support women with myasthenia gravis and their physicians in their decision-making regarding desire for children, the course of pregnancy and delivery and neonatal considerations. With thorough advice, good preparation and support of partners and families, the desire for a child can come true for patients with myasthenia gravis. Taking special precautions and with interdisciplinary treatment, the risks for mother and child can be minimized.

Pregnancy Planning

Due to the peak frequency of myasthenia gravis pseudoparalytica among young women, family planning and the desire for children are a common topic in the context of the treatment of these patients. In principle, the disease does not rule out pregnancy [1]. There is no genetic risk of autoimmune myasthenia in offspring of myasthenia patients.

As with other chronic conditions, pregnancy planning, pregnancy and childbirth require comprehensive coaching of women and their partners and families, as well as a high level of expertise on the part of the attending physicians. The level of ignorance and anxiety is often high among patients and relatives, which is reflected in their decision whether to have children. Therefore, physicians have an important role in educating about the effects of myasthenia on pregnancy and vice versa, drug therapies and childbirth planning as well as postpartum treatment [2]. The myasthenia patient, her partner and family must be fully informed about the chronic disease, prevention and treatment of exacerbation, as well as regarding the specifics of pregnancy, childbirth and postnatal period. In particular, joint responsibility for pregnancy and the child as well as clear rules for the division of responsibilities in family duties are more important than in any other contemporary partnership.

Pregnancy should be delayed one to two years after the initial diagnosis of myasthenia, so that the severity of the disease can be estimated, the optimal individual therapy can be determined and, if necessary, the positive effect of thymectomy can be exploited. Thymectomy is indicated in juvenile patients in the course of generalized AChR antibody-positive myasthenia gravis, and always if a thymoma is detected [3, 4].

Contraception Methods

Oral hormonal contraception is possible in patients with myasthenia gravis, as well as vaginal, subcutaneously implanted preparations or intrauterine devices. The choice of the optimal method should be decided with the gynecologist, taking into account other comorbidities. Current literature does not provide information regarding the sustained influence of contraceptives on myasthenia

[5, 6]. A new, non-hormonal contraceptive and optimized conception method is cycle monitoring by means of the OvulaRing®. This is a plastic ring inserted into the vagina with an integrated biosensor and a reader to be connected to a PC. Using closely-monitored temperature measurement, an algorithm generates a chart of the fertility cycle (cyclofertilogram) which calculates the ovulation and fertility window with 99 % accuracy [7].

Menstruation Cycle

Up to 2/3 of women notice a slight worsening of their myasthenic symptoms prior to and during menstruation [1, 8]. Thus, continuous use of oral contraceptives is recommended [9, 10].

Desire for Children and Drug Treatment

The fear of a harmful effect of the medication on the unborn child is the most common reason for myasthenia patients to avoid pregnancy [2]. During pregnancy planning, the drug therapy must be critically reconsidered, especially the use of immunosuppressants [1, 3, 4]. Drug therapy with cholinesterase inhibitors can be continued without risk. Corticosteroids should be used in the smallest possible dose (less than 15 mg/day). In principle consistent contraception should be used during immunosuppressive therapy. In the absence of an alternative, immunosuppression can be continued with azathioprine in individual cases. Based on current experience, use of cyclosporin A and tacrolimus can be continued [3, 11], but the dosage should be reduced to the lowest required dose. Methotrexate, cyclophosphamide and mycophenolate mofetil are strictly contraindicated due to their severe effects and must be discontinued at least 3 months prior to pregnancy [3]. There is less experience regarding rituximab, thus according to the manufacturer's recommendation, it should be discontinued 12 months prior to, as well as during, pregnancy [11, 12]. The recommendations regarding immunosuppressive therapy also apply to male patients with myasthenia who wish to procreate. Pre-therapeutic sperm preservation should be undertaken due to influence of immune suppression on sperm production [3].

Myasthenia and Pregnancy Interaction

Basically myasthenia has no influence on pregnancy [1]. Duration of pregnancy, birth weight or risk of miscarriage are unaffected [2–4]. Employment is generally not prohibited, but discontinuation should be considered at the start of pregnancy for patients with an unstable course of the disease.

Pregnancy does not worsen the long-term course of myasthenia; in the first trimester and in the postpartum period, the risk of exacerbation is increased by up to 30 % [3, 4, 13, 14]. Stabilization occurs in the second and third trimesters, most likely due to maternal immune depression. During pregnancy, myasthenia-boosting medications should be avoided, and infections should be properly treated.

Maternal myasthenia gravis rarely results in arthrogryposis multiplex congenita syndrome, which due to maternal antibodies against the fetal isoform of the acetylcholine receptor, and phenotypically ranges from myopathy (fetal acetylcholine receptor inactivation syndrome) to the most severe skeletal deformities, and has a high risk of recurrence [3, 15, 16].

Neonatal myasthenia occurs in 10–20 % of newborns due to diaplacental transmission of myasthenia-specific antibodies [3].

Drug Therapy

In oral doses up to 600 mg/day, pyridostigmine poses no teratogenic risk [1]. Intravenous administration should be avoided due to some risk of uterine contractions resulting from its effect on the smooth muscles [1]. Pyridostigmine or neostigmine can be administered parenterally in cases of hyperemesis gravidarum [4].

Immunosuppressive Therapy during Pregnancy

In low quantities, corticosteroids do not pose a teratogenic risk [17]. Prednisone, prednisolone and methylprednisolone do not penetrate the placenta, however, in the first trimester they present an increased risk of cleft palate [17]. It is recommended not to exceed a dose of 15 mg/day [9].

In principle, azathioprine, cyclosporin A, tacrolimus and also rituximab can be used during pregnancy under considerable restrictions and with the strictest risk-benefit considerations.

Mycophenolate mofetil, methotrexate and cyclophosphamide have definitely be discontinued 3 months prior to conception [3, 4]. If pregnancy occurs while the patient is taking methotrexate, mycophenolate mofetil or cyclophosphamide, therapy must cease immediately. The patient should be thoroughly advised regarding teratogenic risk, and comprehensive prenatal diagnostics performed [3, 4].

There is currently no registry which covers the above individual case decisions and with a structure that could provide clear recommendations.

Azathioprine may be continued in pregnancy under careful benefit-risk assessment in the case of a need for continued immunosuppression and severe myasthenia. However, preterm birth and lower birth weight are more common [19]. Observation of more than 1000 pregnant woman using azathioprine showed no increase in malformations [19, 20]. In the liver, azathioprine is converted into the active metabolite 6-mercaptopurine. The fetal liver is not able to convert this [21]; therefore protection against teratogenic effects in early pregnancy is assumed. Normal fetal development should be monitored using high-resolution ultrasound [11].

Likewise, **cyclosporin** A has shown no increased risk of malformations in more than 1000 pregnancies, despite significant teratogenicity in animal experiments. Therefore similar recommendations should be followed as for azathioprine [11].

Mycophenolate mofetil has been shown to be teratogenic in animal experiments. It is advised to discontinue MMF at least 3 months prior to pregnancy [11, 4]. According to scientific information, there is also a risk of damage for male patients.

Methotrexate has a teratogenic effect. MTX has to be discontinued 3 months before the start of pregnancy, and no later than confirmation of pregnancy [11]. Norwood [13] advises a 3-month wash-out phase prior to conception, although the use of folic acid

should be continued [3]. Two studies of women who became pregnant while on MTX showed no observable embryopathy, but there was an increase in spontaneous miscarriage and a significant rate of gross structural abnormalities. Due to the ambiguous body of data, men should use contraception at least 3–6 months prior to attempting conception [22]. Another recent study shows the influence of MTX on in vitro oocyte maturation; significant abnormalities were evident in the MTX group [23].

Cyclophosphamide is a cytotoxic substance, crosses the placenta and was teratogenic in animal experiments. Therefore it is advised that both men and women discontinue the medication 6 months before attempting conception. If pregnancy occurs there is an increased risk of miscarriage and embryopathy [11, 21]. If the pregnancy continues and use of the drug is not suspended, blood count changes and premature birth can occur.

Rituximab In principle, contraception should be used by both the man and woman for at least 12 months before attempting conception. The drug crosses the placenta; if it is continued during pregnancy, B- and CD19+ cells will be depleted in the child for about 6 months [11]. A recent overview article [24] on the use of rituximab for myasthenia gravis describes 2 patients who bore healthy babies despite using the medication. There is the risk of a slightly lower birth weight, premature birth and malformations, which also applies to other monoclonal antibodies (e. g. belimumab) [25]. Thus it is a case-by-case decision, based on the known unstable myasthenia gravis, how to proceed with treatment during pregnancy.

Eculizumab has been recently approved, thus there are no clinical data regarding its effect on pregnancy in cases of myasthenia gravis. Eculizumab crosses the placenta and thus may potentially cause terminal complement inhibition in fetal circulation. In isolated cases, the substance has been successfully used in hemolytic uremic syndrome during pregnancy [26].

Tacrolimus is a macrolide of Streptomyces which is used as an immunosuppressant in transplantation medicine. There are currently no indications of teratogenicity; in the course of pregnancy, women with transplants showed an increased incidence of pre-eclampsia, preterm birth, lower birth weight, and caesarean section, possibly due to the underlying disease. Hyperkalemia and transient kidney function deficiencies have been observed in newborns [11]. Therefore women showing stability with tacrolimus should not be switched to another medication.

Myasthenic Crisis during Pregnancy

Intravenous immunoglobulins are recommended in the treatment of severe myasthenic dysfunction that does not respond to pyridostigmine and low-dose prednisolone. During severe exacerbation or myasthenic crisis, administration of polyvalent immunoglobulins for myasthenia gravis pseudoparalytica is approved and unproblematic during pregnancy (0.4 g/kg bw/d for 5 days). Compared to plasmapheresis and immunoadsorption, the effect is slower, which may promote complications from long-term ventilation and intensive care management. Depending on gestational age, class IgG immunoglobulins cross the placenta; however, fetal damage has not occurred in all previously described treatments during pregnancy [3, 4]. Plasmapheresis and immunoadsorption are considered possible during pregnancy [1, 3, 13].

HELLP Syndrome and Eclampsia

HELLP syndrome (**H**emolysis – **E**levated **L**iver enzymes – **L**ow **P**latelet count) and eclampsia are pregnancy-related life-threatening diseases which have to be promptly treated as such. Alpha-methyldopa (first-line drug) for lowering blood pressure does not exacerbate myasthenia. Benzodiazepines are contraindicated for myasthenia. Magnesium exacerbates myasthenia by inhibiting calcium-dependent presynaptic acetylcholine release. Since eclampsia is a life-threatening disease, prompt therapy must be performed urgently in a hospital with neurological and anesthesiological expertise. Treatment of HELLP syndrome using heparin, acetylsalicylic acid, plasmapheresis or immunoglobulins is possible with respect to myasthenia [3, 4, 13, 18].

CASE 1

- Third pregnancy 2013, 37 years old
- Diagnosis myasthenia (MGFA IIIb in progression IV) 2011, AChR antibodies 30 pmol/l
- Minimally invasive thymectomy 2011: Thymoma (MASAOKA II, WHO B1)
- 2011 Myasthenic crisis with intensive medical therapy, ventilation, plasmapheresis
- 2011–2013 sufficient symptom control, therapy using pyridostigmine, prednisolone and azathioprine, last due to side effects, max. 50 mg/d
- 05/2012 and 08/2013 spontaneous abortions
- 10/2013 IVIG therapy for exacerbation with dysphagia and stress-related physical weakness (AChR antibodies 21 pmol/l)
- 11/2013 onset of 3rd pregnancy. Continuation of 75 mg azathioprine with adequate tolerance and stable clinical myasthenia since then.
- C-section delivery in 37th week, mild respiratory difficulty in otherwise healthy newborn (AChR antibodies 6.5 pmol/l), 1 day neonatal monitoring.
- Good tolerance of delivery (AChR 28 pmol/l), sedative and postpartum. Ablactation due to azathioprine.

Childbirth

Pregnant myasthenia patients should be closely observed by neurologists experienced with myasthenia as well as gynecologists. Delivery should be performed in a full-service clinic where collaboration among experienced gynecologists, anesthesiologists, neurologists and neonatologists with a suitable monitoring unit can be ensured. In principle, spontaneous birth is possible as well as use of epidural anesthesia, which eases the birth and prevents early exhaustion of the mother. It is worth noting that myasthenia has no effect on labor, as smooth muscles are not affected. However, exhaustion of the involved abdominal muscles can lead to a delay in the expulsion phase [1].

In individual cases C-section can be performed when there is premature myasthenia-related exhaustion [3, 4]. It should be noted that if general anesthetic is used, up-to-date, non-polarizing muscle relaxants must be used, and their rate of application should be

determined by means of neuromuscular monitoring [27–29]. Likewise, the use of opiates for pain therapy should be undertaken very carefully because of possible respiratory depression of mother and child [3, 4]. Individual, myasthenia-specific medication should be continuously sustained [30, 31].

After delivery the mother should be monitored depending on the individual case. Because of the risk of postpartum exacerbation, intensive care surveillance should be available [3, 4]. It should be further noted that postpartum infections may occur, resulting in worsening of the myasthenia gravis [3, 4, 32].

CASE 2

- First pregnancy 2013, 26 years old
- 2006 Diagnosis myasthenia (MGFA 2B AChR antibody-positive)
- 2009 myasthenic crisis, therapy with pyridostigmine, prednisolone, azathioprine
- Thymectomy 2009 – thymic hyperplasia
- Drug-based remission using pyridostigmine and azathioprine
- 2010 Azathioprine discontinued due to bacterial endocarditis
- Until 2013 remission using pyridostigmine monotherapy (60– 120 mg/d)
- Unassisted labor 37th week (full-care hospital, gynecological clinic with Level I perinatal center)
- Hypotrophic male newborn, 2345 g, 46 cm
- No spontaneous postpartum respiration, mask, then CPAP ventilation, sufficient independent respiration after 8 min
- General muscle hypotonia, sucking and swallowing not possible
- Therapy with pyridostigmine iv, resulting in significant improvement
- AChR antibodies in newborn > 13.0 pmol/l
- Inpatient treatment until 19th day postpartum, pyridostigmine orally
- On day 30 postpartum, outpatient treatment, hearty crying, spontaneous movement, still no strong mouth closing, oral nutrition possible, weight gain to 3050 g
- Afterward gradual reduction/discontinuation of pyridostigmine therapy
- No exacerbation of myasthenia in mother during pregnancy or immediately afterward

Transient Neonatal Myasthenia Gravis

Ten to twenty percent of children of mothers with myasthenia gravis develop transient neonatal myasthenia gravis, which is marked by weak muscle tone, weak crying and sucking as well as – in rare cases – respiratory insufficiency. Therefore delivery at a hospital with a neonatal unit is necessary. Maternal antibodies crossing the placental barrier cause this condition [1, 33, 34]. According to their half-life, the symptoms resolve within 8–16 weeks, but may also include therapy, e. g. with pyridostigmine or neostigmine, rarely require temporary mechanical ventilation. In one case report immunoglobulins were not effective [35]. There are neither predictive factors for the development of transient neonatal myasthenia, nor are there any for the risk of repetition after successive pregnancies [1].

Postpartum and Lactation

Breast feeding is possible if the mother is on a low dosage of pyridostigmine and prednisolone [3, 4]; both pass into the mother's milk, however. Due to the risk to pediatric hormone production, higher dosages should be avoided during lactation [1]. Because of its half-life, it is advisable to take prednisolone immediately after breastfeeding and to plan the next breastfeeding approximately 4 h later. The following information is available for azathioprine: Norwood [13] does not see any contraindication; www.embryotox.de [11] recommends blood level monitoring for the child and does not entirely rule out breast feeding while azathioprine is used. Both cyclosporin A and tacrolimus may be acceptable during lactation if good pediatrician support can be assured, since these substances hardly pass into mother's milk [21]. Cyclophosphamide passes substantially into the mother's milk, however [21], therefore mothers treated with MTX or rituximab should definitely not breastfeed.

Organizing Daily Life with Newborns

The stress of childbirth, a possible worsening of myasthenia postpartum and infant care possibly around the clock represent a particular challenge for myasthenic patients. Stress and disturbed sleep can result in accentuated muscular fatigue.

Already during pregnancy, division of tasks should be discussed with the partner and family. Information should be sought regarding aid from the health insurance, and possibly from self-help groups and the youth welfare office [36]. Clarification regarding domestic help should be sought from the health insurance company at an early stage and the related application obtained. Midwife support can be helpful. In particular physical rest should be a part of planning daily activities. The partner's parental leave may be useful, particularly in the first weeks after the birth [36]. Basically during the postpartum period the frequency of developing myasthenia gravis is increased [32].

SUMMARY

Good preparation, appropriate precautions, detailed counseling and interdisciplinary treatment, as well as the support of partners and family make it possible for myasthenia patients to become pregnant while maintaining low risks for mother and child.

Conflict of Interest

A. Thieme declares no conflicts of interest. P. Kalischewski discloses receiving consulting and lecture fees as well as expense reimbursement from Novartis, Genzyme, Biogen und Teva for participation in registries and non-interventional studies.

References

[1] Köhler W, Sieb JP. Myasthenia gravis. 4. Auflage. Bremen: UNI-MED Verlag; 2012

[2] Ohlraun S, Hoffmann S, Klehmet J et al. Impact of myasthenia gravis on family planning: How do women with myasthenia gravis decide and why? Muscle Nerve 2015; 52: 371–379

[3] Klehmet J, Ohlraun S, Meisel A. Myasthenia gravis und Schwangerschaft. Akt Neurol 2014; 41: 447–453

[4] Klehmet J, Dudenhausen J, Meisel A. Verlauf und Behandlung der Myasthenia gravis in der Schwangerschaft. Nervenarzt 2010; 81: 956–962

[5] Leitenberger F, Strowitzki T, Ortmann O. Klinische Endokrinologie für Frauenärzte. 5. Auflage. Heidelberg: Springer Verlag; 2014

[6] Gnoth C, Mallmann P. Perikonzeptionelle Frauenheilkunde. Heidelberg: Springer-Verlag; 2014: 153–155

[7] Alexander H, Kaczmarczyk MA, Schiwek E. OvulaRing. Das Cyclofertilogramm (CFG) zur exakten Zyklus- und Fertilitätsdiagnostik. Ärztebl Sachsen 2015; 26: 539 – 542

[8] Sieb JP. Myasthenie und Schwangerschaft. Newsletter Myasthenie Kolloqium 2006; 2 Temmler ZNS

[9] Röhmer T, Görentzlehner G. Kontrazeption mit OC in 160 Problemsituationen. Berlin: de Gruyter Verlag; 2012

[10] www.embryotox.de Arzneimittelsicherheit in Schwangerschaft und Stillzeit, Pharmakovigilanz- und Beratungszentrum für Embryonaltoxikologie; Augustenburger Platz 1, 13353 Berlin

[11] Hoff JM, Daltveit AK, Gilhus NE. Myasthenia gravis: Consequencies for pregnancy, delivery, and newborn. Neurology 2003; 61: 1362–1366

[12] Norwood Dhanjal M, Hill M et al. Myasthenia in pregnancy: Best practice guidelines from a UK multispecialty working group. J Neurol Neurosurg Psychiatry 2014; 85: 538–543

[13] de Meel R, Lipka AF.van Zwet Prognostic factors for exacerbation and emergency treatments in myasthenia gravis. J Neuroimmunology 2015; 282: 123–125

[14] Hoff JM. Maternal myasthenia gravis: A couse for arthrogryposis multiplex. J Child Orthop 2015; 9: 433–435

[15] Hacohen Y, Jacobson LW, Byrne S et al. Fetal acetylcholine receptor inactivation syndrome: A myopathy due to maternal antibodies. Neurol Neuroimmunol Neuroinflamm 2014; 2: e57

[16] Reuner U, Dinger J. Lambert-Eaton-Syndrom und Schwangerschaft. Newsletter Myasthenie Kolloqium 2011; 1 Temmler ZNS

[17] Hoffmann S, Kohler S, Zieglr. A Glucocorticoids in myasthenia gravis- if, when, how, and how much? Acta Neurol Scand 2014; 130: 211–221

[18] Varner M. Myasthenia gravis and pregnancy. Clin PObst Gynecolo 2013; 56: 372–381

[19] Armenti V, Radomski JS, Moritz MJ et al. Report from the National Transplantation Pregnancy Regestry (NTPR): Outcomes of pregnancy after transplantation. Clin Transpl 2003; 131–141

[20] Moskovitz DN, Bodian C, Chapman ML et al. The effect on the fetus of medications used to treat pregnant inflammatory bowel-disease patient. Am J Gastroenterol 2004; 99: 656–661

[21] Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy and lactation. Arch Intern Med 2000; 160: 610–619

[22] Gutierrez JC, Hwang K. The toxicity of methotrexate in male fertility and paternal teratogenicity. Expert Opin Drug Metab Toxicol 2017; 1: 51–58

[23] Tian N, Yu J, Zhang S et al. Effects of methotrexate on the qualitiy of oocyte maturation in vitro. Eur Biophy J 2017, doi:10.1007/s00249-017-1254-2 [Epub ahead of print]

[24] Stieglbauer K, Pichler R, Topakian R. 10-year outcomes after rituximab for myasthenia gravis: Efficacy, safety, costs of inhospital care, and impact on childbearing potential. J Neurol Sci 2017; 375: 241–244

[25] Ostensen M. The use of biologics in pregnant patients with rheumatic disease. Expert Rev Clin Pharmacol 2017; 6: 661–669

[26] Hallstensen RF, Bergset S, Foss S et al. Eculizumab treatment during pregnancy does not affect the complement system activity of the newborn. Immunobiology 2015; 220: 452–459

[27] Schwab S, Krieger D, Müllges W et al. Neurologische Intensivmedizin. Berlin: Springer Verlag; 1999

[28] Walz R, Lubbe N, Walz K et al. Muskelrelaxation mit Atracurium bei Myasthenia gravis. Anaesthesiol Reanim 1996; 21: 43–46

[29] Blobner M, Mann R. Anästhesie bei Patienten mit Myasthenia gravis. Anaesthesist 2001; 50: 484–493

[30] Banerjee A, Wilson I.Anaesthesia and myasthenia gravis. anaesthesia tutorial of the week, World Federation of Societies of Anaestesiologists 2008 http:/totw.anaestesiologists.org/2008/12/14/anaesthesia-and-myasthenia-122/ (accesed online:10/05/2011)

[31] Gambling D, Douglas M, McKay R. Obstetric anaestesia and uncommon disorders. Cambridge UK: Cambridge University Press; 2008

[32] Boldingh M, Maniaol AH, Brunborg C et al. Increased risk for clinical onset of myasthenia gravis during the postpartum period. Neurology 2016; 87: 2039–2045

[33] Statland JM, Ciafaloni E. Myasthenia gravis. Five new things. Neurol Clin Pract 2013; 3: 126–133

[34] Licht U, Model P, Kribs S. Transiente neonatale Myasthenia gravis. Nervenarzt 2002; 73: 774–778

[35] Tagher RJ, Baumann R, Desai N. Failure of intravenously administered immunoglobulin in the treatment of neonatal myasthenia gravis. J Pediatr 1999; 134: 233–235

[36] Bundesministerium für Familie, Senioren, Frauen und Jugend: Assistenz bei der Familienarbeit für behinderte und chronisch kranke Eltern. broschuerenstelle@bmfsfj.bund.de