Continuing Medical Education

Pregnancy and Autoimmune Disease

Diseases of the Nervous System, Connective Tissue, and the Bowel

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Summary

Background: Pregnancies in women with chronic disease are on the rise. This pertains to autoimmune diseases in particular since these tend to affect women of childbearing age. The interaction between pregnancy and autoimmune disease may increase the risk of maternal, fetal, and obstetric complications; additional care may be required.

Methods: This review is based on a selective literature search in PubMed (2015–2020).

Results: In women with autoimmune diseases, the course of pregnancy is highly variable. Some autoimmune diseases tend to improve during pregnancy and do not to result in any serious obstetric complications. Others may worsen during pregnancy, with deterioration of the maternal condition as well as obstetric and perinatal complications. In systemic lupus erythematosus and myasthenia gravis, placental transfer of specific autoantibodies may cause fetal or neonatal disease.

Conclusion: The care of pregnant women with chronic diseases requires collaboration between specialists of the pertinent levels of care. A stable course of disease before conception, close interdisciplinary care, and pregnancy-compatible medication contribute to a reduction in maternal and perinatal complications.

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Advances in the treatment of chronic diseases and the associated higher quality of life and life expectancy allow affected couples the opportunity to fulfill their desire to start a family. Furthermore, methods of reproductive medicine are available for those diseases that are often associated with subfertility.

It is no surprise, therefore, that a steady increase has been observed in recent decades in the number of pregnancies in women with chronic diseases. A Danish registry study reported a rise in prevalence from 3.7% to 15.8% between 1989 and 2013; a four- to eight-fold rise was demonstrated for the autoimmune diseases rheumatoid arthritis (from 0.1% to 0.73%), systemic lupus erythematosus (from 0.02% to 0.07%), chronic inflammatory bowel disease (from 0.3% to 1.09%), and multiple sclerosis (from 0.04% to 0.26%) (1). In a German investigation for the period 2002–2008, 21.4% of all pregnant women reported having a chronic disease (2).

Pregnancies in women with a preexisting disease are potentially high-risk pregnancies and are associated with a higher rate of maternal and obstetric complications. A recent US investigation of almost 1.5 million births found a 4.8-fold higher rate of severe maternal complications among women with preexisting diseases (0.5% severe complications in women

Prevalence

The prevalence of pregnancies in women with chronic diseases is continuously rising. This applies in particular to autoimmune diseases, given that these affect predominantly women of childbearing age.

Preexisting diseases

Maternal deaths due to preexisting diseases are more frequent than those due to direct causes of death (such as, for example, hemorrhage or puerperal sepsis).

without preexisting disease, 5.6% in the case of ≥ three comorbidities) (3). The same trend can be seen for maternal deaths: whereas direct causes of death such as preeclampsia, thromboembolism, or hemorrhage used to dominate the statistics, preexisting diseases or non-obstetric diseases that manifest for the first time during pregnancy have been the leading cause of maternal mortality for over 20 years (4).

Autoimmune diseases are characterized by a preponderance for females, as well as first manifestation during the reproductive phase. Thus, they are among the commonest preexisting diseases in pregnancy. At the same time, anticipated disease courses are highly variable, ranging from an improvement in symptoms, for example in rheumatoid arthritis, to an exacerbation involving maternal and fetal complications, as in systemic lupus erythematosus.

Although the causes of these differences are unclear, they have been linked to the complex immunological changes that take place during pregnancy. These are characterized by an immune tolerance to the paternally inherited antigens expressed by the fetus or trophoblast cells (e1). Obstetric complications typically comprise variably increased rates of miscarriage, intrauterine fetal death, fetal growth restriction, and preterm birth. The long-term effects arising from the altered intrauterine environment are increasingly attracting research attention; these relate to, for example, the development of cardiovascular and metabolic disorders (e2–e5).

Learning objectives

After reading this article, the reader should:

- Be familiar with the principles of care of pregnant women with autoimmune diseases of the nervous system, connective tissue, and the bowel, and be able to identify the special features that arise as a result.
- Be aware of the options with regard to maternal and fetal monitoring in pregnancies of women with these preexisting diseases.
- Have gained knowledge of the various courses of disease and pregnancy as well as their treatment options.

Care

According to the preexisting disease, affected women are treated by representatives of various levels of care. In the case of pregnancy, this team expands to include experts in maternal and fetal medicine as well as high-risk obstetrics. For some diseases, the respective German guidelines make reference to action pathways. However, maternity guidelines do not elaborate on the care of pregnant women with preexisting diseases (5).

The goal is a care plan that includes preconception counseling, as well as treatment during pregnancy, birth, and into the postpartum period. This also includes close collaboration between levels of care. It is important to ensure a care team with designated contacts, especially in complex cases where there is a high risk of complications in the course of pregnancy. Centralized care in institutions with appropriate expertise is another element that leads to a better outcome for both mother and newborn and is recommended for pregnant women with severe disease courses (e6).

An essential requirement for a successful course of pregnancy is stable disease before conception. Therefore, women with chronic diseases should plan their pregnancy. Furthermore, preconception counseling should take place to discuss, among other things, any anticipated interactions between the preexisting condition and pregnancy, as well as to review medications.

Pharmacological treatment during pregnancy and breastfeeding is characterized by three problems:

- Use of a potentially teratogenic drug during an unplanned and possibly unnoticed pregnancy
- Discontinuation of an indicated drug without medical consultation after pregnancy confirmation due to fear of a harmful effect on the unborn child
- Limited knowledge of the teratogenicity and/or fetotoxicity of drugs.

Very few drugs cause a clearly recognizable malformation pattern. Most birth defects have multifactorial origins, and indications of a teratogenic effect of a drug arise from the increase in relative risk. For an adequate assessment, the European Medicines Agency requires prospectively collected data from at least 1000 pregnancies associated with exposure in the first trimester (6). On the other hand, there is uncertainty with regard to several diseases as to whether the disease itself or the drugs used increase the risk of birth defects (e7, e8).

Ultimately, the prescription of drugs during pregnancy calls for special diligence and should be based on current data as well as the individual's medical history and disease course, as established during a consultation (e9). The replacement of the FDA classes with the Pregnancy and Lactation Labeling Rule (7) takes this into account.

The following is a review of selected neurological, connective tissue, and gastroenterological autoimmune

Incidence

Autoimmune diseases are among the commonest preexisting diseases in pregnancy.

Preventive medical care

In the presence of chronic disease, pregnancy should be planned and care provided by a multidisciplinary team.

TABLE 1

Pregnancy, birth, and the puerperium in autoimmune diseases of the nervous system, connective tissue, and the bowel

Autoimmune disease	Prevalence in women of childbearing age	Common autoimmune comorbidities	Typical disease course during pregnancy	Risk factors for pregnancy complications	Obstetric complications (miscarriage, PTB, FGR)	Special aspects of delivery	Typical disease course in the puerperium
Multiple sclerosis	2:1000 Around 250,000 cases in Germany; women affected three times more often	Type 1 DM, TG, IBD, psoriasis	Flare risk reduced by up to 80% in 3rd trimester of pregnancy without immunomodulatory therapy in the year preceding pregnancy; disease activity common during pregnancy if certain highly effective therapies are discontinued	Active disease during pregnancy	Not increased	None	Flare risk increased for 3–4 months postpartum
Myasthenia gravis	1:10,000–1:50,000	TG, RA, SLE	Improvement in 20% of cases, stable or worse in 80% of cases	Previous pregnancy with arthrogryposis	FGR risk increased	Consider instrumental delivery; stress/exertion avoidance; neonatal monitoring, since 10–20% develop transient neonatal MG	Symptom worsening in around a third of cases
Neuromyelitis optica spectrum disorders	Unknown in Germany; women significantly more affected (3:1–9:1)	TG, Sjögren's syndrome, SLE, MG	Evidence not yet conclusive as to whether flare risk already rises in the last trimester, postpartum rise in flares	Active disease during pregnancy	Risk of miscarriage increased in active disease	None	Flare risk increased postpartum
Rheumatoid arthritis	2–4:1000	TG, Sjögren's syndrome, uveitis	48–60% Improvement, 40% stabile or worse	Active disease during pregnancy	Increased rate of SIH/PE, FGR, PTB, DVT	Increased CS rate	Flare risk increased postpartum (ca. 40–50%)
Systemic lupus erythematosus	55:100,000	Sjögren's syndrom, APS, TG	Around one- to two-fold higher risk of flares; ~25% mild to moderate; 5% severe	Active disease 6–12 months before or during pregnancy; LN; aPL, HCQ discontinuation	Increased rates of miscarriage (associated with aPL), SIH/PE, FGR, PTB, DVT; SS-A/SS-B Ab: congenital AV block (1–2%), neonatal lupus	Increased CS rate	Flare risk postpartum around one- to two-fold higher for 6 months
Primary Sjögren's syndrome	No reliable data	TG	No effect	–	Increased rates of miscarriage, SIH/PE, FGR, PTB; SS-A/SS-B Ab: congenital AV block (1–2%), neonatal lupus	Increased CS rate	No reliable data
Systemic sclerosis	No reliable data	TG	Very limited data, dependent on disease severity/activity	Rapidly progressive diffuse disease	Increased FGR, PTB	Increased CS rate	No reliable data
Axial spondyloarthritis	No reliable data	Psoriasis, IBD, uveitis	No effect	–	No consensus regarding link	Increased CS rate	Flare risk not increased
Crohn's disease and ulcerative colitis	3–4:1000	IBD-associated arthritis, erythema nodosum, pyoderma gangrenosum, PSC, AIH, inflammatory eye disease	A third of patients develop flare activity	Active disease 6–12 months prior to conception	Increased rate of miscarriage, FGR, PTB	CS in preexisting or active perianal Crohn's disease; avoid episiotomy (?)	Increased flare risk postpartum (due to paused medication?)

AIH, autoimmune hepatitis; Ab, antibodies; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; AV block, atrioventriclar block; CS, cesarian section; IBD, inflammatory bowel diseases; DM, diabetes mellitus; FGR, fetal growth restriction; HCQ, hydroxychloroquine; LN, lupus nephritis; MG, myasthenia gravis; PE, preeclampsia; PSC, primary sclerosing cholangitis; PTB, preterm birth; RA, rheumatoid arthritis; TG, autoimmune diseases of the thyroid gland; PIH/PE, pregnancy induced hypertension/preeclampsia; SLE, systemic lupus erythematosus; SS-A/SS-B Ab, SS-A/Ro, and SS-B/La antibodies; DVT, deep vein thrombosis

diseases with regard to their care in the context of pregnancy, childbirth, and the puerperium. The tables provide an overview of the diseases *(Table 1)*, the drugs used *(eTable)*, and fetal monitoring *(Tables 2 and 3)*.

Multiple sclerosis and neuromyelitis optica spectrum disorders

The therapeutic spectrum of neuroimmunological diseases has significantly widened in recent years, which explains why pregnancy planning has a special role to play. The *eTable*, summarized from Krysko et al. (8) and Mao-Draayer et al. (9) provides an overview of the approved immunotherapies as well as the special approach used during pregnancy and lactation. If pregnancy occurs while a woman is on teratogenic medication, she should immediately present to a center for detailed counseling; detailed ultrasound examinations are also advised.

Multiple sclerosis primarily affects women and is diagnosed in young adulthood in more than two-thirds of cases. Interestingly, the incidence has been rising particularly among women in recent decades (e10). Pregnancies in women with multiple sclerosis are usually unaffected by the underlying disease, with no increased risk of a negative pregnancy outcome. Birth weight is lower compared to neonates born to healthy mothers (10). Pregnancy in affected patients usually leads to a reduction in the rate of flares in the final third of pregnancy and an increase in the first months following birth. Disease activity during pregnancy depends on the activity of the underlying disease as well as on the timing of discontinuation of the various immunotherapies (8). Pregnancies do not affect the long-term prognosis of the disease.

Stabilizing the disease prior to pregnancy is beneficial. Recent data suggest that using drugs with a prolonged biological effect in multiple sclerosis can also protect against disease activity during pregnancy (8, 11). Mild flares in multiple sclerosis (without relevant functional impairment) during pregnancy need not be treated with corticosteroids. In the case of severe flares, high-dose cortisone should be administered, or immunoadsorption or plasmapheresis carried out.

Mode of delivery and type of anesthesia do not affect the rate of flares in pregnant women with multiple sclerosis. Women with this disease should be supported in their wish to breastfeed. Breastfeeding does not increase the postpartum risk of flares. Preliminary results of as yet small cohorts in recent studies indicate that breastfeeding is still possible off-label during monoclonal antibody treatment (12) *(eTable)*.

Neuromyelitis optica spectrum disorders represent a very rare spectrum of neuroimmunological diseases that follow a course involving flares and which affect in particular women. They can be associated with an increased rate of pregnancy complications (miscarriages), as well as severe flares. These disorders are listed in *Table 1* as a separate entity. From a treatment perspective (azathioprine, mycophenolate mofetil, rituximab, satralizumab, eculizumab), there is a considerable overlap with other autoimmune diseases.

Myasthenia gravis

Myasthenia gravis has a bimodal age distribution with two peaks of incidence (in the third decade and after the sixth decade), with predominantly females affected in the younger age group. A distinction is made between a generalized and an ocular form, the latter having a better prognosis. An increased associated risk of preterm birth is mooted, but otherwise pregnancy complications do not appear to be increased (13, 14). A very recent analysis of US insurance data points to more respiratory complications in the mother and longer hospital stays (healthy women: 0.1%; women with myasthenia gravis: 2.26%) (15).

The course of myasthenia gravis in pregnancy varies widely from individual to individual. While the condition remains stable in many pregnant women, it can also worsen, and in a small proportion of women even improve. Worsening occurs in the first or second trimester and/or after birth.

Myasthenic crisis in pregnancy should be managed according to general treatment guidelines, for example, intravenous immunoglobulins or plasmapheresis (13, 14), and treated as an emergency by an interdisciplinary team. In the general treatment of myasthenia gravis, the lowest effective steroid dose should be selected. The administration of magnesium for preeclampsia in affected pregnant patients can lead to a critical worsening.

For the identification, diagnosis, and differential diagnosis of maternal disease-specific symptoms and complications, close cooperation should be ensured between experts in neurology, fetal and maternal medicine, as well as neonatology in the case of active disease.

Vaginal delivery is recommended also for women with myasthenia gravis; however, the mode of delivery should depend on the overall condition, i.e., respiratory/motor fatigue. Smooth muscle fibres, and

Discontinuing certain highly effective multiple sclerosis drugs

The discontinuation of certain highly effective multiple sclerosis drugs can sometimes lead to an aggressive exacerbation of disease activity, despite the known immunomodulatory effects of pregnancy.

Effects in myasthenia gravis

Magnesium for the treatment of preeclampsia can cause a worsening of myasthenia gravis.

TABLE 2

Recommended prenatal tests for the purposes of diagnosis and monitoring*

Disease	First trimester	Second trimester	Third trimester	Other investigations	Special aspects
Multiple sclerosis, neuromyelitis optica spectrum diseases, rheumatoid arthritis, systemic sclerosis, axial spondyloarthritis, Crohn's disease, ulcerative colitis	Appt. I; optional: FTS, NIPT, PES	Appt. II; optional FMS	Appt. III; optional: US 34th–36th GW	–	–
Myasthenia gravis	Appt. I; optional: FTS, NIPT, PES	Appt. II; optional FMS	Appt. III; optional: US 34th–36th GW	From 24th GW, 4–6-weekly monitoring of fetal joint position and motor function	–
Systemic lupus erythematosus, primary Sjögren's syndrome	Appt. I; optional: FTS, NIPT (PES unneccessary, since ASA indicated)	Appt. II; FMS, UtA-DU, EchoCG	Appt. III; optional: US 34th–36th GW	In SS-A Ab: from 16th GW weekly fetal heart rate monitoring and fetal EchoCG in 20th GW	In CCHB: EchoCG every 2 weeks; in FGR, abnormal UtA-DU and other signs of placental insufficiency: growth and Doppler scans

*Maternity guidelines generally specify ultrasound screening (ultrasound screening I, II, and III at around 10th, 20th, and 30th GW, respectively) (e45–e48, 5).
The investigations referred to as optional are not specified in the maternity guidelines and are only conducted in the case of an appropriate indication, but are considered medically beneficial and should be performed—after providing detailed information about their advantages and disadvantages and the associated consequences, as well as obtaining consent from the patient. In addition, FTS, NIPT, and IPT are subject to the special requirements set out in the German Genetic Diagnostics Act (*Gendiagnostikgesetz*).
Appt., appointment; ASA, acetylsalicylic acid; CCHB, complete congenital heart block (third-degree AV block); EchoCG, fetal echocardiography; FGR, fetal grwoth restriction; FMS, fetal malformation screening (= detailed ultrasound examination for fetal malformations); FTS, first trimester screening (aneuploidy screening + fetal malformation screening); GW, gestational week; IPT, invasive prenatal diagnosis; NIPT, noninvasive prenatal testing (analysis of cell-free deoxyribonucleic acid in maternal blood); PES, preeclampsia screening; SS-A Ab, SS-A/Ro antibodies; US, ultrasound screening; UtA-DU, Doppler ultrasound of the uterine arteries (preeclampsia screening in the second trimester)

thus uterine contractions, are not affected. However, muscular or perhaps also respiratory exhaustion may occur in the course of labor, potentially making vaginal operative delivery or cesarean section necessary.

Wherever possible, regional anesthetic techniques should be preferred. Epidural anesthesia is also possible. Certain drugs, such as a number of antibiotic classes as well as benzodiazepines, can exacerbate myasthenia gravis and should not be used *(Box)*. Special fetal aspects resulting from the transplacental passage of pathogenic antibodies in myasthenia gravis are described in the section "Fetal monitoring."

Rheumatoid arthritis

The prevalence of rheumatoid arthritis in women of childbearing age is around 0.2%. Women with rheumatoid arthritis have an approximately one-and-a-half to two-fold increased risk of hypertensive complications in pregnancy (7–10%), fetal growth restriction (15–20%), preterm birth (10–12%), and cesarean delivery (20–42%), even after adjusting for parity (16, 17). Venous thromboembolism occurs between two and four times more frequently than in healthy pregnant women (0.2–0.4%). Preterm birth and growth restriction have been associated with disease activity and higher glucocorticoid doses.

Rheumatoid arthritis activity tends to be favorably affected by pregnancy. Studies using validated instruments to measure disease activity found signs of improvement during pregnancy in 48–60% of women with previously active rheumatoid arthritis (18). Following delivery, 39–50% experienced a flare. For women wishing to become pregnant, conception should be planned for a time when disease activity is absent or low; in addition, maintenance therapy that is compatible with both pregnancy and lactation should be continued if possible, particularly in view of the high risk of flares following birth (19). Long-term pediatric sequelae due to the mother's disease are not known.

Systemic lupus erythematosus

The initial manifestation of systemic lupus erythematosus predominantly occurs before the age of 30 years. Prevalence is estimated to be 55 per 100,000 in the female population. The incidence of fetal, maternal,

Recommendations on delivery planning in patients with myasthenia gravis

Vaginal birth is possible; however, the mode of delivery should depend on the overall clinical condition. Smooth muscle fibres, and thus uterine contractions, are not impaired.

Recommendation on family planning counseling

Women with connective tissue diseases who wish to fall pregnant should receive individual and interdisciplinary care prior to conception.

TABLE 3

Approach for pregnant women with known SS-A/Ro antibodies and for women diagnosed with fetal congenital complete heart block (CCHB)

Clinical situation	Approach	CCHB prevention	CCHB incidence	Fetal treatment	Other
Asymptomatic pregnant women with known SS-A/Ro and/or SS-B/La Ab (without CCHB/NLE in a previous child)	16th–24th GW, weekly fetal HR monitoring*1 Fetal echocardiography around the 20th GW	HCQ ≤ 10th GW for a purely fetal indication controversial*2 (possible adverse effects in NNT of ≥ 100)	1–2%	Not required In case of second-degree AV block, attempt rescue therapy*3	SS-A/Ro Ab are found in 2–3% of women of childbearing age In the first days of life, neonatal ECG to document normal sinus rhythm
Symptomatic pregnant women with known SS-A/Ro and/or SS-B/La Ab (without CCHB/NLE in a previous child)	16th–24th GW, weekly fetal HR monitoring Fetal echocardiography around the 20th GW	Continue HCQ ≤ 10th GW for a maternal indication	1–2%	Not required In case of second-degree AV block, attempt rescue therapy*3	In the first days of life, neonatal ECG to document normal sinus rhythm
Pregnant women with known SS-A/Ro and/or SS-B/La Ab and CCHB in a previous child	16th–24th GW, weekly HR checks Echocardiographic monitoring every 1–2 weeks	HCQ beginning ≤ 10th GW: reduction in recurrence risk from 16–19% to 7–8% Preventive treatment with fluorinated corticosteroids, IVIG, or plasmapheresis without effect	16–19%	In case of second-degree AV block, attempt rescue therapy*3	In the first days of life, neonatal ECG to document normal sinus rhythm
Pregnancy with incidental finding of CCHB (70% of cases of autoimmune-mediated CCHB)	Ab determination (SS-A/Ro and SS-B/La-AK) Echocardiographic monitoring every 1–2 weeks	Not applicable	Not applicable	Treatment with fluorinated corticosteriods, also in combination with IVIG, discussed controversially due to side effects*4; possibly indicated in case of impending cardiac deterioration, as in ventricular dysfunction, AV valve insufficiency, myocardial calcification, endocardial fibroelastosis	Maternal SS-A/Ro and/or SS-B/La Ab detectable in > 90% ; in 20–30% of cases, asymptomatic pregnant women. Survival rate in CCHB 80%; death in approximately 20%: ca. 15% antenatally (fetal heart failure and hydrops) and ca. 5% postnatally (mostly due to dilatative cardiomyopathy); pacemaker required in 70% of newborns; 10-year survival in liveborn infants of 90%
Pregnancy with CCHB in known SS-A/Ro and/or SS-B/La Ab (30% of cases of autoimmune-mediated CCHB)	Echocardiographic monitoring every 1–2 weeks				

Ab, antibodies; AV, atrioventricular; CCHB, congenital complete AV block (third-degree AV block) EchoCG, echocardiography; HCQ, hydroxychloroquine; HR, heart rate; IVIG, intravenous immunoglobulin; NLE, neonatal lupus erythematosus; NNT, number needed to treat; GW, gestational week; SS-A/SS-B Ab, SS-A/Ro and SS-B/La antibodies;

*1 The expectation that weekly measurements of fetal AV intervals (e49) between 16+0 and 24+6 GW—the time at which CCHB mostly commonly manifests—would detect the development of first-degree AV block, thereby preventing higher-degree AV block by subsequent treatment with corticosteroids, has not been fulfilled (e34, e50, e51). The same applies to home monitoring of fetal heart rate (e33, e54).

*2 Proarrhythmic QTc prolongation should be seen as a risk in HCQ treatment, particularly in combination with other drugs used in pregnancy, such as azithromycin, ondansetron, antihistamines, and antidepressants (e56); pregnancy-related low magnesium, calcium, and vitamin D may increase this risk (e56). However, the incidence of QTc prolongation was not elevated in newborns of pregnant women receiving HCQ treatment (e57). In the low-risk collective (pregnant women with SS-A/Ro Ab without a previous child with CHB), due to the potential for proarrhythmic QTc prolongation as a result of HCQ in the pregnant woman and fetus (2% of fetuses have QTc times > 500 ms) at an NNT of ≥ 100, the use of HCQ for purely fetal preventive indications should be carefully considered and is not indicated in asymptomatic women with low titers (e56).

*3 Prior to the irreversible manifestation of CCHB, second-degree AV block may occur in a brief transitional phase (< 12–24 h); this is reversible with and without dexamethasone therapy in 25% of cases. In this short transitional phase, rescue therapy with high-dose dexamethasone combined with IVIG may be able to increase the remission rate or prevent progression to CCHB (e52–e55). Since weekly echocardiographic examinations are insufficient for this due to the short time window, home monitoring of the fetal heart rate several times a day is proposed for the early detection of second-degree AV block and the initiation of immediate rescue therapy—however, without any significant success to date (e33, e54, e55).

*4 Transplacental high-dose treatment with fluorinated corticosteroids to improve myocarditis and subsequent cardiomyopathy is controversial, given that its effect on outcome is uncertain (e34-e36) and that it is associated with adverse maternal and fetal side effects, such as impaired growth, brain development, and fetal programing, i.e., permanent physiological and metabolic changes that predispose to cardiovascular, metabolic, and endocrine disease in adulthood (e37).

and obstetric complications is significant; in addition to preterm birth and growth restriction, these include preeclampsia and thromboembolic disease (20). Disease activity is one of the most important risk factors. For example, the likelihood of preterm birth rises from 5.5% to 33.3% in the case of active systemic lupus erythematosus (21). The highest risk for preterm birth and preeclampsia arises from a combination of high clinical and serological activity. The risk is also increased in the case of positive antiphospholipid antibodies (aPL) and lupus nephritis. The likelihood of flares rises by 60% in pregnant compared to non-pregnant patients. This risk depends on disease activity prior to conception. Treatment with hydroxychloroquine reduces the rate of flares. How good the chances are for a pregnancy with few complications in stable systemic lupus erythematosus is demonstrated by the PROMISSE study, in which 80% of pregnancies had an uncomplicated course and severe flares occurred in only 5% of cases (22). The special fetal aspects resulting from the detection of autoantibodies to the ENA antigens SS-A/Ro and SS-B/La are explained in the section "Fetal monitoring" as well as in *Tables 2 and 3*. The same applies to women with primary or secondary Sjögren's syndrome.

Antiphospholipid syndrome develops in the setting of systemic lupus erythematosus in approximately 20% of affected individuals. Antiphospholipid antibodies are associated with a higher risk of thrombosis and obstetric complications, most notably late miscarriage and placental insufficiency. Depending on the clinical and serological constellation, treatment consists of acetylsalicylic acid (ASA) and/or heparin (23).

Pregnancy in systemic lupus erythematosus should be planned after 6–12 months of absent or mild disease activity. During the preconception phase, treatment should be reviewed and an acceptable immunosuppressive therapy either continued or switched to in order to maintain remission. After a change in medication, tolerance and efficacy needs to be followed-up for 6 months. Hydroxychloroquine should always be continued or, if not contraindicated, newly initiated. Low-dose ASA for preeclampsia prevention is recommended in all patients.

In the case of renal involvement, it is best to plan pregnancy during inactive lupus nephritis (at least 6 months), namely, proteinuria <0.5 g/day, normal renal function, and normal blood pressure. In pregnancy, active nephritis is sometimes challenging to distinguish from preeclampsia, since an increase in proteinuria and blood pressure can be suggestive of both. Here, for example, evidence of erythrocyturia, a fall in complement, and symptoms typical of systemic lupus erythematosus should be considered. Acceptable immunosuppressive treatment should also be continued in this situation in order to maintain remission.

Chronic inflammatory bowel disease

The prevalence of chronic inflammatory bowel diseases, Crohn's disease and ulcerative colitis, is 300 and 400/100 000, respectively, with a peak incidence in the third/fourth decade of life (e11). In the past, many patients with these disorders were extremely reluctant regarding pregnancy and/or continuing disease-specific medication for fear of an unfavorable course (e12). There is evidence from older studies that these patients, as an overall cohort, have a somewhat higher risk for growth restriction and premature birth (e13).

Disease activity at the time of conception has the strongest effect on disease course during pregnancy. Therefore, current guidelines advise that conception be planned during a period of remission. However, the question of how long remission should have been stable remains unanswered—a period of around 6 months can be considered as realistic (24, 25). Under these conditions, about one-third of patients experience a flare during pregnancy. A recent study observed a significantly reduced incidence of recurrence when targeted treatment for inflammatory bowel disease was ongoing at the time of conception (26). This was associated with lower rates of hospitalization and prematurity as well as higher birth weights. On the other hand, active inflammatory bowel disease at the time of conception is associated with preterm birth, growth restriction, and, in all likelihood, a higher rate of early miscarriage (e14).

The long-term disease course is somewhat milder as a result of pregnancy (e15). During the postpartum period and lactation, there is an increased risk of flare that correlates with disease activity in the third trimester and possible treatment de-escalation during pregnancy and in the postpartum phase (e16).

Patients with perianal involvement should receive proctologic treatment in addition to primary, internal medical/gastroenterological, and obstetric/prenatal care. Visceral surgical co-treatment is reasonable in the presence of (intermittent) symptoms of bowel obstruction (25).

The drugs currently used do not have any negative effects on fertility in patients with inflammatory

Systemic lupus erythematosus

The incidence of fetal, maternal, and obstetric complications is significant. One of the most important risk factors is systemic lupus erythematosus activity prior to pregnancy.

Planned pregnancy in systemic lupus erythematosus

Pregnancy in systemic lupus erythematosus should be planned after 6–12 months of absent or mild disease activity.

BOX

Infobox with important addresses

Pharmacovigilance and Advisory Center for Developmental Toxicology
www.embryotox.de

Advisory service on drugs during pregnancy and lactation
www.uniklinik-ulm.de/frauenheilkunde-und-geburtshilfe/schwerpunkte/geburtsmedizin/medikamentenberatung.html

Portal for rare diseases and orphan drugs Orphanet
www.orpha.net/consor/cgi-bin/index.php

Multiple sclerosis (MS) and family planning
www.ms-und-kinderwunsch.de; k.hellwig@klinikum-bochum.de

Geman Multiple Sclerosis Society
plan-baby-bei-ms.dmsg.de

Registers in Germany:
German-language MS and family planning register (DMSKW)
www.ms-und-kinderwunsch.de/projektbeschreibung.html

Myasthenia and pregnancy
www.dmgkw.de

Rheumatic diseases, family planning, and pregnancy (Rhekiss)
rhekiss.de

Scientific Working Group on Pediatric Anesthesia of the DGAI (German Society of Anesthesiology and Intensive Care Medicine)
www.dgai.de/kinderanaesthesie

Recommendations on anesthesia in myasthenia gravis
www.orpha.net/data/patho/Ans/de/Myasthenia-gravis-DE.pdf

bowel disease. Methotrexate is used to maintain remission, but is strictly contraindicated in pregnancy and must be discontinued at least 3 months prior to conception.

Malnutrition is not an uncommon problem in patients with inflammatory bowel disease; therefore, screening and, if necessary, targeted interventions should be performed before as well as during pregnancy and lactation (27). The German Nutrition Society (*Deutsche Gesellschaft für Ernährung*) recommends that women take 550 µg/day folic acid as early as 4 weeks prior to conception and during the first trimester. According to the European guideline, iron (or ferritin) and folic acid levels should be monitored and, where necessary, supplemented in high doses (27). In addition to oral iron preparations, which are often poorly tolerated by these patients, modern dextran-free intravenous iron preparations represent an effective and well-tolerated substitution therapy for use in the second and third trimesters (28).

Clinical signs of increased disease activity are challenging to differentiate from symptoms that often develop during pregnancy, such as abdominal pain, nausea, rectal bleeding from hemorrhoids, and symptoms of anal stenosis/constipation. Fecal calprotectin—in contrast to hemoglobin, C-reactive protein, and albumin—is not altered by pregnancy and, as such, appears to be suitable as a predictor of impending flares (e17). Gastrointestinal ultrasound correlates well with fecal calprotectin and has a reliable negative predictive value of approximately 0.9; however, from the 20th gestational week onwards, it is often not possible to adequately visualize the terminal ileum (e18). Since endoscopy is usually not required to make a treatment decision, it should only be performed if strongly indicated (29, e19). In combination with pregnancy-related changes, scar tissue stenosis can progress to subileus or ileus, which may require resection.

With regard to delivery, the European guideline advises avoiding episiotomy, citing the risk of fistula formation (24). The few retrospective studies that have been conducted do not confirm this risk, but these must be interpreted with caution due to a possible selection bias; this also applies to the indication for elective cesarean section in patients with ileal pouch anal anastomosis (30). Crohn's disease with manifest perianal fistulas or Crohn's proctitis are indications for elective cesarean section.

If a mother is affected, the child's risk of developing Crohn's disease or ulcerative colitis is 2.7% and

Risk in chronic inflammatory bowel disease

The highest risk for complications in pregnancy arises as a result of active inflammatory bowel disease ("flare") at the time of conception.

Malnutrition in patients with chronic inflammatory bowel diseases

Malnutrition is not an uncommon problem in patients with inflammatory bowel disease; therefore, screening and, if necessary, targeted interventions should be performed before as well as during pregnancy and lactation.

3.7%, respectively (e20). There is no evidence of a developmental delay in the child as a result of targeted inflammatory bowel disease therapy during pregnancy (31).

Fetal monitoring

The extent and methods of fetal monitoring are based on the individual risk of the pregnant woman, depending on her general and reproductive history as well as risks over the course of pregnancy *(Table 2)*.

Risks in pregnant women with autoimmune diseases that require extended fetal diagnosis and monitoring are predominantly placenta-related disorders (preeclampsia/growth restriction), most notably in systemic lupus erythematosus and, according to recent data, likely also in Sjögren's syndrome; less frequently, effects of drug therapy pose a risk.

The extent of growth restriction, gestational age, Doppler findings, and symptoms determine the intervals for the monitoring of fetal growth and wellbeing (e21, e22). Multimodal preeclampsia screening in the first trimester can predict the development of preeclampsia before the 37th gestational week in 75% of cases (e23) and reduce it by 60% in this high-risk group of patients through the administration of 150 mg ASA/day starting before the 16th week of gestation (e24). In the case of systemic lupus erythemathosus, the maternal risk factors are so severe that in the absence of preeclampsia screening, ASA prophylaxis should be given from 12 weeks' gestation until birth (32, 33, e25–e28); due to the increased rate of peripartum maternal as well as neonatal intracerebral hemorrhage in some studies, this should be given only until the 36th week of gestation (e29, e30).

Transplacental transfer of IgG autoantibodies to the fetus occurs from around the 13th gestational week (e31). SS-A/Ro antibodies are present in 30–40% of pregnant women with systemic lupus erythematosus and in 60–70% of those with Sjögren's syndrome. Together with SS-B/La antibodies, these can cause neonatal lupus erythematosus. Symptoms such as skin lesions, anemia, and thrombocytopenia are reversible postnatally upon the disappearance of maternal antibodies, but complete congenital heart block (CCHB)—often the only symptom of neonatal lupus erythematosus—is not. CCHB has high perinatal mortality as well as short- and long-term morbidity *(Table 3)* (34, 35, e32, e33).

Whereas anti-Ro52 (SS-A) antibodies can induce inflammation in the conduction system, and even myocarditis, Ro60 and La48 antibodies can have a modifying effect (e33-e37, 34, 35). *Table 3* contains information on the management of pregnant women with known SS-A/Ro antibodies as well as on the diagnosis of immune-mediated CCHB in the fetus.

In the case of myasthenia gravis, acetylcholine receptor (AChR) autoantibodies that cross the placenta may decrease the number and/or function of AChR at the motor end-plate. AChR consists of two α-subunits, one β-, one δ-, and one γ-subunit (fetal form) in developing muscle fibers and, from the 30th gestational week, one ε-subunit (adult form) in the developed muscle fibers (e38). Maternal autoantibodies are mostly directed against the α-subunit. They can cause transient congenital myasthenia in 10–20% of newborns, characterized by hypotension, weak suckling, dysphagia, weak crying, and, in rare cases, respiratory weakness and aspiration. Acetylcholinesterase inhibitor therapy is indicated in such cases (14, 36, e39).

More rarely, autoantibodies are directed against the fetal γ-subunit. These may be present in isolation in asymptomatic pregnant women and cause fetal AChR inactivation syndrome (e40) in the form of arthrogryposis multiplex, rarely also fetal akinesia deformation sequence with multiple joint contractures and pulmonary hypoplasia (36, e39), as well as myopathy (e40, e41). The prenatal diagnosis in myasthenia gravis includes a careful assessment of joint position and motor function (e41).

Conflict of interest statement

Prof. Fischer Betz received honoraria for consultancy work from UCB. She received honoraria for lectures from Abbvie, Biogen, BMS, Chugai, GSK, Novartis, Medac, MSD, Pfizer, and UCB. She received travel cost reimbursement from Abbvie, Biogen, BMS, Chugai, GSK, Novartis, Medac, MSD, Pfizer, and UCB. She is a member of the board of the DGRH. She received writing support from UCB.

Prof. Hellwig received honoraria for consultancy work from Biogen, Roche, Merck, and Genzyme. She received reimbursement of congress participation fees from Biogen, Teva, Novartis, Roche, and Merck. She received travel cost reimbursement from Biogen, Teva, Novartis, and Merck. She received honoraria for preparing scientific advanced training events from Bayer, Biogen, Teva, Novartis, Roche, and Merck. For conducting clinical trials, she received funds from Merck, Roche, and Biogen. She received funds from Biogen, Bayer, Genzyme, Merck, Novartis, Teva, and Roche for a research project of her own initiation.

The remaining authors declare that no conflict of interests exists.

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Development of placenta-related diseases

In pregnant women with systemic lupus erythematosus and, according to the most recent data, likely also those with Sjögren's syndrome, the risk of developing a placenta-related disease (preeclampsia and fetal growth restriction) is significantly increased.

Risk in pregnant women with systemic lupus erythematosus and Sjögren's syndrome

In these patients, SS-A/Ro and/or SS-B/La antibodies can be transferred to the fetus, leading to neonatal lupus erythematosus; autoimmune-mediated complete AV block is irreversible.

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► **Supplementary material**

eReferences, eTables:
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Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

What is the current prevalence of pregnancies in women with chronic diseases?

a) 3–8%;
b) 6–11%
c) 9–14%;
d) 12–17%
e) 15–21%

Question 2

What precautions should women with autoimmune diseases and a wish to conceive take with regard to pregnancy?

a) As early as prior to conception, they should avoid all forms of physical exertion.
b) They should discontinue all medications 6 months prior to a planned pregnancy.
c) They should plan their pregnancy and be cared for by a multidisciplinary team.
d) They should take high-dose vitamin C and D supplements in advance of a pregnancy.
e) They should achieve pregnancy by means of in-vitro fertilization.

Question 3

What effect does pregnancy have on rheumatoid arthritis disease activity?

a) It leads to an improvement in 20% of cases.
b) It leads to an improvement in 50–60% of cases.
c) It leads to a worsening in 20% of cases.
d) It leads to a worsening in 55–60% of cases.
e) As a general rule, no change in disease activity is seen.

Question 4

What are common autoimmune comorbidities in pregnant women suffering from rheumatoid arthritis?

a) Autoimmune disorders of the thyroid and Sjögren's syndrome
b) Primary sclerosing cholangitis and antiphospholipid syndrome
c) Ulcerative colitis and lupus nephritis
d) Systemic lupus erythematosus and Crohn's disease
e) Antiphospholipid syndrome and lupus nephritis

Question 5

Which investigation should be performed in a pregnant woman with myasthenia gravis from the 24th week of gestation?

a) Weekly fetal heart tracing
b) Monitoring of fetal joint position and motor function at intervals of 4–6 weeks
c) Weekly growth monitoring
d) Weekly Doppler ultrasound of the placenta
e) Organ ultrasound of the fetus every 2 weeks

Question 6

Multimodal preeclampsia screening in the first trimester is able to predict preeclampsia in many cases. Which intervention is able to significantly reduce the risk of preeclampsia?

a) Relaxation exercises and autogenic training
b) Regular participation in antenatal classes
c) Administration of 10 mg/day simvastatin
d) Administration of 150 mg/day acetylsalicylic acid
e) Physical rest from the 16th gestational week

Question 7

You see persistent fetal bradycardia (60 bpm) on ultrasound in a 30-year-old primigravida in the 21st gestational week, with otherwise normal findings. Which tests do you order?

a) A virological test to exclude a fetal infection as the cause of bradycardia
b) Doppler ultrasound scan of the umbilical artery in order to exclude severe placental insufficiency as the cause of bradycardia
c) Fetale echocardiography to differentiate bradycardia, as well as testing for the presence of SSA/Ro antibodies in maternal blood
d) Drug history, since some drugs cause marked, persistent fetal bradycardia
e) Microbiological tests to exclude a fetal infection as the cause of bradycardia.

Question 8

You are attending to a 32-year-old primigravida with systemic lupus erythematosus. Which investigations do you order in addition to ultrasound screening?

a) Preeclampsia screening in the 12th gestational week, in order to initiate preventive acetylsalicylic acid treatment in the case of increased risk for the development of preeclampsia
b) Ultrasound and Doppler ultrasound monitoring of fetal growth and status, since the risk of placental insufficiency is increased
c) Glucose tolerance testing every 3 months, since the risk of gestational diabetes mellitus is increased
d) Serological tests every 3 months for cytomegalovirus, parvovirus B19, and toxoplasmosis, since the risk of initial infection or reinfection with these is increased
e) Regular vaginal examinations and pH measurements in order to promptly identify and prevent impending preterm birth

Question 9

When are women with inflammatory bowel disease (IBD) at highest risk for complications during pregnancy?

a) If disease activity is high at the time of conception
b) If nicotine is consumed during pregnancy
c) If medication for active IBD is used during pregnancy
d) If the patient is overweight at the time of conception
e) If there is a history of cesarean section

Question 10

Which drug is absolutely contraindicated during pregnancy?

a) Mesalazine; b) budesonide
c) prednisolone; d) methotrexate
e) azathioprine

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Supplementary material to:

Pregnancy and Autoimmune Disease

Diseases of the Nervous System, Connective Tissue, and the Bowel

by Waltraut Maria Merz, Rebecca Fischer-Betz, Kerstin Hellwig, Georg Lamprecht, and Ulrich Gembruch

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eTABLE

Drugs for the treatment of autoimmune diseases of the nervous system, connective tissue, and the bowel during pregnancy and lactation (e42, 8, 9, e43, e44)

	Mode of action	Teratogenicity/ fetotoxicity	Approach in planned pregnancy/during pregnancy*1	Special aspects when used during pregnancy (dose adjustment, monitoring)	Breast-feed-ing*2
Corticosteroids					
Prednisone Prednisolone	T-cell inhibition	FGR	Continue; select lowest effective dose	Intensified blood glucose monitoring	1
Budesonide	T-cell inhibition + first-pass effect liver	No information	Continue	–	2
Conventional immunosuppressants					
Azathioprine	Antimetabolite	If used in 3rd trimester, bone marrow suppression possible in the newborn	Continue	In the case of leukopenia in the pregnant woman in the 3rd trimester, the dose should be reduced, if possible, and a FBC performed in the newborn	2
6-Mercaptopurine	Antimetabolite	If used in 3rd trimester, bone marrow suppression possible in the newborn	Continue	In the case of leukopenia in the pregnant woman in the 3rd trimester, the dose should be reduced, if possible, and a FBC performed in the newborn	2
Colchizine	Mitosis inhibition	Not known	Continue	.	2
Cyclosporine	Calcineurin inhibitor	FGR	Continue	Maximum dose 3.5 mg/kg/BW/day	5
Hydroxychloroquine	Incompletely understood; immunomodulatory	No information	Continue	.	2
Tacrolimus	Calcineurin inhibitor	FGR	Continue	Intensified blood glucose monitoring; drug level determinations	2
Cyclophosphamide	Antimetabolite	Characteristic human teratogenic birth defect pattern is discussed	Discontinue (≥ 3 months) before conception	Consider use in life-threatening complications from the 2nd trimester onwards	8
Mycophenolate mofetil	Antimetabolite	High potential for characteristic human teratogenic birth defect pattern	Discontinue > 6 weeks before conception	Contraindicated	8
Methotrexate	Antimetabolite	High potential for characteristic human teratogenic birth defect pattern, also teratogenic in antirheumatic doses	Discontinue 1–3 months before conception; preconceptional start of folic acid substitution (1–5 mg/day)	Contraindicated	8
Leflunomide	Antimetabolite	Teratogenic in animal models; insufficient human data, no significant teratogenicity as yet in ca. 900 pregnancies	Discontinue and accelerate elimination before planned pregnancy	Contraindicated	7
Teriflunomide	Antimetabolite	Teratogenic in animal models; insufficient human data, no significant teratogenicity as yet in <300 pregnancies	Discontinue and accelerate elimination before planned pregnancy or in accidental exposure	Contraindicated	7
Cladribine	Antimetabolite	Teratogenic in animal models; insufficient human data	Discontinue 6 months before conception	Contraindicated	8
Mitoxantrone	Anthracycline	Teratogenic and fetotoxic	Discontinue 6 months before conception	Contraindicated	8
Novel substances					
Natalizumab	Integrin-α4 Ab	Limited human data	Discontinue upon positive PT; case-by-case decision if disease activity is high	If used in the 3rd trimester, FBC of the newborn	4

Adalimumab	TNF-α Ab	No information	Discontinue in 3rd trimester; case-by-case decision if disease activity is high	If used in the 3rd trimester, no live vaccine for the first 6 months of life	3
Certolizumab	Fab-fragment of a recombinant, humanized monoclonal TNF-α Ab	No information	Can be continued throughout pregnancy due to little or no placental transfer	Due to lack of data when used in the 3rd trimester, no live vaccine for the first 6 months of life	3
Etanercept	Human TNF-α fusion protein	No information	Discontinue in 3rd trimester; case-by-case decision if disease activity is high	If used in the 3rd trimester, no live vaccine for the first 6 months of life	3
Golimumab	Human monoclonal TNF-α Ab	No information	Discontinue in 3rd trimester; case-by-case decision if disease activity is high	If used in the 3rd trimester, no live vaccine for the first 6 months of life	4
Infliximab	Chimeric monoclonal TNF-α Ab	No information	Discontinue in 3rd trimester; case-by-case decision if disease activity is high	If used in the 3rd trimester, no live vaccine for the first 6 months of life	1
Rituximab	Anti-CD20 Ab	Limited human data; if used in the 2nd + 3rd trimester, B-cell depletion possible in the newborn	According to product information, discontinue 12 months before conception; in individual cases, earlier conception recommended if disease activity is high	Live vaccine only once B-cells have normalized in the infant	7
Ocrelizumab	Anti-CD20 Ab	Fetotoxic in animal models	According to product information, discontinue 12 months before conception; in individual cases, earlier conception recommended if disease activity is high	Live vaccine only once B-cells have normalized in the infant	-
Ofatumumab	Anti-CD20 Ab	Limited human data	According to product information, discontinue 6 months before conception; in individual cases, earlier conception recommended if disease activity is high	Live vaccine only once B-cells have normalized in the infant	4
Belimumab	Human monoclonal IgG Ab against B-lymphocyte stimulator protein (BLyS/BAFFt)	Limited human data	Case-by-case decision if disease activity is high	No data or specific recommendations on live vaccines in newborns	3
Abatacept	Fusion protein combining the extracellular domain of human CTLA4 and a modified Fc region of human IgG1	Limited human data	Case-by-case decision if disease activity is high	No data or specific recommendations on live vaccines in newborns	7
Tocilizumab	IL-6 receptor Ab	Limited human data	Case-by-case decision if disease activity is high	No data or specific recommendations on live vaccines in newborns	4
Anakinra	IL-1 receptor Ab	Limited human data	Case-by-case decision if disease activity is high	No data or specific recommendations on live vaccines in newborns	3
Apremilast	Phosphodiesterase inhibitor	Very limited human data	Discontinue or switch before conception	–	7
Tofacitinib	JAK1/3 inhibitor	Teratogenic in animal models, very limited human data	Discontinue or switch before conception	–	7
Baricitinib	JAK1/3-p	Teratogenic in animal models, very limited human data	Discontinue or switch before conception	–	–
Upadacitinib	JAK1 inhibitor	Teratogenic in animal models, no human data	Discontinue or switch before conception	–	–
Vedolizumab	α4/β7 Integrin Ab	Very limited human data	Case-by-case decision if disease activity is high	No data or specific recommendations on live vaccines in newborns	4
Ustekinumab	Human monoclonal IL-12/23 Ab (IgG1)	Very limited human data	Case-by-case decision if disease activity is high	No data or specific recommendations on live vaccination in newborns	7

Alemtuzumab	CD52 Ab	Fetotoxic in animal models	Discontinue 4 months before conception	–	7
Eculizumab	C5 complement Ab	Limited human data	Case-by-case decision if disease activity is high	–	3
Specific MS drugs					
Interferon-β	Immunomodulation	Fetotoxic in animal models, much human data on 1st trimester exposure with no evidence of teratogenicity	Discontinue upon positive PT; continue if disease activity is high	–	2
Glatiramer acetate	Immunomodulation	Much human data on 1st trimester exposure with no evidence of teratogenicity	Discontinue upon positive PT; continue if disease activity is high	–	3
Dimethyl fumarate	Immunomodulation	Fetotoxic in animal models	Discontinue before conception, at latest upon positive PT	–	4
Fingolimod	Immunosuppression	Teratogenic and fetotoxic	Discontinue ≥ 2 months before conception	Contraindicated	4
Siponimod	Immunosuppression	Teratogenic and fetotoxic	Discontinue ≥ 10 days before conception	Contraindicated	–
Ozanimod	Immunosuppression	Teratogenic and fetotoxic in animal models	Discontinue ≥ 3 months before conception	Contraindicated	–
Ponesimod	Immunosuppression	Teratogenic and fetotoxic in animal models	Discontinue 1 week before conception	Contraindicated	–
Specific MG drugs					
Pyridostigmine/ neostigmine	Acetylcholinesterase inhibitor	Fetotoxic in animal models	Continue; select lowest effective dose	Maximum dose 600 mg/day	3
NSAIDs					
COX-1 inhibitors	Antiinflammatory	Premature closure of the ductus arteriosus	Can be continued up to 28th GW	Discontinue after 28th GW; if used continuously from the middle of the 2nd trimester, check amniotic fluid volume and blood flow profile in ductus arteriosus	3
COX-2 inhibitors	Antiinflammatory	Premature closure of the ductus arteriosus; limited human data	Avoid	Avoid	3
Aminosalicylates					
Mesalazine	Antiinflammatory	No information	Continue	–	6
Salazosulfapyridine	Antiinflammatory	No information	Continue; begin folic acid substitution before conception (1–5 mg/day)	Maximum dose 2 g/day	6
Others					
Immunoglobulins		Not expected	Can be used during pregnancy	–	4

Ab, antibodies; CD, cluster of differentiation; COX, cyclooxygenase; FBC, full blood count; FGR, fetal growth restriction; IgG, immunoglobulin G; IL, interleukin; JAK, Janus kinase; MG, myasthenia gravis; MS, multiple sclerosis; NSAIDs, non-steroidal antiinflammatory drugs; PT, pregnancy test; GW, gestational week

*1 According to risk–benefit analysis, e.g., depending on disease severity and activity, as well as after detailed individual consultation

*2 1, Compatible; 2, probably compatible; 3, limited human data, probably compatible; 4, no human data, probably compatible; 5, potential toxicity; 6, limited human data, potential toxicity; 7, no human data, potential toxicity; 8, contraindicated