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Review

Multiple sclerosis and pregnancy

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Key content

- Multiple sclerosis (MS) is a chronic neurological disease that manifests with clinical and subclinical attacks of central nervous system demyelination.
- Women are at least twice as likely as men to develop MS, with a mean age of onset of 30 years.
- Pregnancy has no adverse long-term effect on disease progression, but it is associated with a higher relapse rate in the immediate postpartum period.
- Pregnancy can worsen pre-existing urinary/bowel dysfunction and motor problems.
- MS is not associated with significant obstetric or neonatal complications.

Learning objectives

- To understand how to manage pregnant women with MS in the multidisciplinary setting.
- To understand the importance of pre-pregnancy counselling for women with MS who are on disease-modifying drugs.
- To understand the implications of pregnancy on MS symptoms and their management.
- To be aware of the benefits of breastfeeding and the safety of disease-modifying drugs and lactation.

Ethical issues

- In the absence of clear guidelines, should women ever be advised to avoid pregnancy?
- Should women be offered in vitro fertilisation treatment, which is known to increase disease relapse?

Keywords: breastfeeding / contraception / disease-modifying drug therapy / multiple sclerosis / regional anaesthesia

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating disorder of the central nervous system that is characterised by neurological relapses and frequent progressive neurological dysfunction and disability. Multiple sclerosis is two to three times more common in women[1,2] than in men, with a mean age of onset of 30 years. More than half of women with MS will develop the disease during their reproductive years, making pregnancy issues important for these patients.[3] A population study by Mackenzie et al. showed that 126 669 people in the UK were living with MS in 2010 and the prevalence among women was 285.8 per 100 000.[1]

Although the aetiology of MS is unknown, genetic components seem to be important.[4] It is difficult to positively identify high-risk individuals using genetic screening because most carriers with the HLA-DRB1*1501 allele[5] are not in the genetically susceptible group.[5] The lifetime risk of developing MS in the general population is 1 in 330. Around 80% of people with MS have an affected family member. Data from a meta-analysis of familial risk studies by O'Gorman et al. showed the risk of inheritance with one affected parent to be 1 in 67, increasing to around 10% with one affected sibling and one affected parent. The risk is highest – at around 20% – in monozygotic twins and in children who have both parents affected. The risk is 5% in dizygotic twins. The recurrence risk with one affected child is 2.7%.[2,6] The remainder of risk is determined by environmental or lifestyle risk factors such as viral infection (e.g. Epstein–Barr virus), smoking and obesity.[7]

MS is categorised on the basis of three patterns of progression and relapse: relapsing remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS). Patients with SPMS can still have the occasional relapse. Most patients (85%) are diagnosed with RRMS, which is characterised by cycles of remission and relapse. Over time, some people develop SPMS whereby relapse

Box 1. Clinical presentation of multiple sclerosis

Primary symptoms – a direct result of damage to the myelin and nerve fibres in the central nervous system

Most common	*Least common*
Fatigue	Dysarthria, dysphonia
Urinary incontinence or retention	Dysphagia
Numbness, tingling/prickling	Seizures
Loss of balance	Tremors
Dizziness and vertigo	Breathing problems
Visual problems: optic neuritis (often the first symptoms in 20–30%), diplopia, blurring of vision, poor colour vision	Itching
	Headache
	Hearing loss
Acute and chronic pain	
Constipation or anal incontinence	
Spasticity	
Cognitive symptoms	
Mood changes: significant clinical depression, mood swings, irritability	

Secondary symptoms – complications as a result of primary symptoms

Recurrent urinary tract infections
Poor postural alignment and trunk control
Decreased bone density (and resulting increased risk of fracture), shallow, inefficient breathing

becomes infrequent but their disabilities worsen. About 10–15% of people are diagnosed with PPMS, in which there is a progressive worsening of the disability from disease onset, with rare occurrences of relapse. The expanded disability status scale (EDSS) is the most widely used scale to monitor disease progression. This is a 20-point scale, ranging from 0 = 'normal' to 10 = 'death caused by MS', marked in 0.5 increments. MS can present with a wide range of symptoms, as summarised in Box 1.

This article gives an overview of the course of the disease during pregnancy, its impact on pregnancy and the safety of medications used to treat MS during pregnancy and breastfeeding.

Effect of pregnancy and breastfeeding on MS

Women with MS appeared to have fewer relapses during pregnancy,[7–9] but relapse during the first 3–4 months postpartum is not uncommon (20–30% of female patients).[10–12] The single best predictor for postpartum relapse is the pre-pregnancy relapse rate.[13,14] MS relapses occur less often in parous women, and pregnancy after MS onset is associated with a lower risk of progression.[9,15] A recent systematic review by McKay et al.[7] confirmed that pregnancy does not alter the risk of MS or long-term progression.

MS was traditionally considered a T cell-mediated autoimmune disease, although recently the role of B cells has been widely recognised and is the basis of several new drugs. During pregnancy, there is a shift from cell-mediated immunity towards increased humoral immunity. Normal pregnancy is associated with predominately T helper 2 (Th2) cytokine response, with interleukin 10 (IL-10) produced by the fetal–placental unit playing a major role in the maintenance of pregnancy. IL-10 production is significantly reduced at term, and this downregulation favours a pro-inflammatory state around the time of labour. This antenatal immunosuppression explains spontaneous remission of MS during pregnancy and exacerbations during the postpartum period.[16]

Pregnancy is associated with worsening of some symptoms of MS, such as fatigue, back pain and bladder/bowel problems. Pregnancy is also associated with a higher incidence of urinary tract infection (UTI), especially in women with a neurogenic bladder.[17–19] Some women with MS and existing mobility difficulties report a further reduction in mobility and increased spasticity as the pregnancy progresses, which is associated with increasing weight and changes in the centre of gravity. Although many of these symptoms are attributed to pregnancy, one must be vigilant for symptoms that might suggest relapse. Most new relapses involve different symptoms that have not presented before, whereas most 'pseudo relapses' manifest as a flare-up of all symptoms, sometimes with greater intensity. For example, the development of painful visual loss (optic neuritis) in a woman who had never experienced visual symptoms before suggests a new relapse, whereas relapse is not suggested in a woman with existing walking difficulties who reports a worsening gait and greater fatigue. New symptoms should be promptly reviewed by the neurologist. Women must be reassured that there is no increased risk of relapse with the use of regional anaesthesia, especially epidural use.[20,21]

Several studies have found that breastfeeding has beneficial effects on MS relapse.[14,22–25] Exclusive breastfeeding for at least the first 2 months postpartum has shown to reduce relapse in the immediate postnatal period[11,14,22,24] as it leads to a distinct hormonal state in which luteinising hormone (LH) and pulsatile gonadotrophin-releasing hormone (GnRH) are suppressed and prolactin levels are high. This results in anovulation, lactational amenorrhoea and a reduction of tumour necrosis factor-alpha (TNF-α)-producing CD4 cells. This immunological effect is believed to reduce postpartum relapse by four-fold.[14,26] A meta-analysis by Papkoor et al. demonstrated that breastfeeding halves the risk of MS relapse.[25] However, the heterogeneity of studies with a lack of differentiation between exclusive and non-exclusive breastfeeding and the severity of disease was not considered in reaching a consensus.

Effects of MS on pregnancy

Maternal effects

Although fertility is not affected by the disease per se, recent evidence from a study by Thöne et al. suggests that anti-Müllerian hormone – the marker for ovarian reserve – is significantly reduced in women with MS.[27] However, MS is associated with a higher frequency of voluntary childlessness (22% versus 13% in women without MS) and many more women with MS will choose to terminate their pregnancy than those without the disease (20% versus 12%).[28] Reasons for voluntary childlessness and termination most often cited in the published literature are disability or fear of disability, fear of transmitting MS to offspring, fear of discontinuing medications and discouragement from physicians. The sexual dysfunction that is reportedly seen in 30–70% of women with MS may also contribute to the rate of voluntary childlessness in this population. In addition, some older immunosuppressants used to treat MS, such as mitoxantrone or cyclophosphamide (which are rarely used in MS treatment currently), can have a negative effect on fertility.

Reassuring results have been found in several studies that have explored maternal outcomes in women with MS.[29,30] A large national database study of 7697 pregnancy outcomes in women with MS showed a higher rate of antenatal hospitalisation and caesarean delivery, when adjusted for maternal age and race. However, they were unable to adjust for other variables such as medication use, duration and severity of underlying disease and parity.[31] A small increase in operative vaginal deliveries has been noted in women with greater disability,[26] which may be associated with worsening neuromuscular weakness.

Fetal effects

There is evidence to suggest no major increase in adverse outcomes in infants born to women with MS. The rate of miscarriage, stillbirth and congenital abnormality are not increased in women with MS.[32] Several studies have shown no increased risk of miscarriage in women with MS who are exposed to disease-modifying therapies (DMTs).[32–34] The risk of congenital malformations of children born to women with MS is comparable to that in the general population.[35] This effect was noted even in women exposed to some, but not all, DMTs.[33,36–38] Women with MS can be reassured that there is no increased risk of stillbirth or perinatal mortality.[17,18,39]

A systematic review and meta-analysis by Finkelsztejn et al.[8] suggested a higher prevalence of prematurity and low birthweight in children born to women with MS. There is a small – albeit increased – risk of preterm delivery before 37 weeks of gestation in women with MS.[17,18] An increased rate of preterm delivery (8.3% versus 6.4%) was noted in women with disease manifestation compared with women without symptoms (whether pre-diagnosis or in the early stages of MS).[39] Several studies have shown an increased risk of fetal growth restriction (FGR) in women with MS.[12,17,18,31] The risk of FGR is approximately 1.7 times higher than that of the general obstetric population.[31] This increased risk is noted in women diagnosed with MS and was not observed in women before the onset of MS.[39]

Safety of the use of MS medications during pregnancy and breastfeeding

It used to be the case that all immunosuppressants and other DMTs for MS were stopped prior to conception. However, growing evidence from pregnancy registries suggests that some DMTs, like glatiramer acetate and interferons, are relatively safe to use during early pregnancy.[40,41] The risk of stopping DMTs must be discussed with patients during pre-pregnancy counselling, usually by the neurologist and the MS nurse who know the patient better. Although the overall risk of a relapse is reduced in pregnancy, for some patients with highly active disease who are taking DMTs, there is the risk of a significant rebound of disease activity (within 3 months). Therefore, there will be a small cohort of women who choose to stay on their DMT, e.g. natalizumab, while pregnant, or – alternatively – who re-start it early in the postpartum period to reduce the risk of a significant postpartum relapse. Other immunosuppressants and DMTs are contraindicated during pregnancy and breastfeeding, either because of their negative effects on the growing fetus or because of limited evidence of safety.

Table 1 provides a summary of the safety of the use of MS medications during pregnancy and breastfeeding to maintain disease remission and treat acute flare.[36,42–59] Definitions of the US Food and Drug Administration (FDA) categories are shown in Box 2.

Pre-pregnancy counselling

So far, no study has shown that pregnancy in MS is harmful, therefore patients can be reassured that pregnancy does not lead to disease progression. Usually, this is discussed with the MS clinical team (neurologists and specialist nurses). When a woman is planning a pregnancy, meeting with the obstetrics team could also reduce the anxiety that is usually felt. For both the patient and the multidisciplinary team, it is usually helpful to summarise the illness and its treatment so far, and to outline possible treatment plans in the event of a relapse during pregnancy. This discussion should include the importance of conceiving during remission and of good disease control during pregnancy to reduce adverse pregnancy outcomes. The impact of the disease on pregnancy and vice versa and the safety of medications used during pregnancy and breastfeeding should also be

Table 1. Safety of medications during pregnancy and breastfeeding

	FDA classification	Pre-conception	Pregnancy	Breastfeeding	Comments
Interferon-β	C	Stop after conception	Contraindicated	Contraindicated	Does not cross the placental barrier No increased risk of congenital abnormalities, spontaneous miscarriage, SGA or preterm delivery with early pregnancy exposure[42]
Glatiramer acetate	B	Stop after conception	Contraindicated	Caution	Does not cross the placental barrier No increased risk of congenital abnormalities, spontaneous miscarriage, SGA or preterm delivery with early pregnancy exposure[43–45]
Steroids	C	Possible	Possible	Possible	Used to treat flare-ups Increased association with maternal hypertension, gestational diabetes, SGA infants, preterm rupture of the membranes, preterm delivery[46] Can cause neonatal adrenal suppression at higher doses Give 'stress dose' at delivery
Natalizumab	C	Stop before conception Maintain effective contraception for 2–3 additional months after discontinuing drug	Although some women are able to discontinue treatment before or during pregnancy, others with more severe disease may elect to continue treatment	Contraindicated	Crosses placenta after second trimester and peaks during third trimester Increased risk of SGA fetus No increased risk of spontaneous miscarriage or fetal malformations[47,48] Known to cause SGA fetus,[47] fetal haematological abnormalities (anaemia/ thrombocytopenia)[49]
Teriflunomide	X	Stop before conception Recommend an accelerated elimination procedure with oral cholestyramine Maintain effective contraception as long as plasma concentration is above 0.02 mg/l	Contraindicated	Contraindicated	Teratogenic in animal studies but not in humans No increased risk of spontaneous miscarriages [50]
Alemtuzumab	C	Stop before conception Maintain effective contraception for 4 months after discontinuation	Contraindicated	Contraindicated	Does not cross placental barrier until week 13 Embryo toxic in animal studies No increased risks of spontaneous miscarriage or teratogenicity in human studies[51]

Table 1. (Continued)

	FDA classification	Pre-conception	Pregnancy	Breastfeeding	Comments
Fingolomid	C	Stop before conception Maintain effective contraception for 2 months after discontinuation	Contraindicated	Contraindicated	Crosses placental barrier Teratogenic in animal studies Increased risk of spontaneous miscarriage rate (24% versus 15%) and higher rate of fetal abnormalities[52,53]
Mitoxantrone	D	Stop before conception Maintain effective contraception for 6 months after discontinuation	Contraindicated	Contraindicated 28 days of clearance	Reduction of ovarian reserve and amenorrhoea[54,55] Fetal growth restriction and preterm delivery in animal models
Methotrexate	X	Stop before conception Maintain effective contraception for 6 months after discontinuation	Contraindicated	Contraindicated	Teratogenic and embryotoxic Increased miscarriage and congenital anomalies with specific pattern[56]
Mycophenolatemofetil	D	Stop before conception Maintain effective contraception for 6 weeks after discontinuation	Contraindicated	Contraindicated	Teratogenic Increased miscarriage and congenital anomalies with specific pattern[57]
Dimethyl fumarate	C	Stop before conception Contraception could be stopped rapidly as short half-life	Contraindicated	Contraindicated	Crosses placental barrier No increased risk of miscarriage, fetal anomalies[36]
Cladribine	D	Stop before conception Maintain effective contraception for 6 months after discontinuation	Contraindicated	Contraindicated	Very limited data Teratogenic in animal studies No increased miscarriage rate, congenital malformation in humans[58]
Ocreluzimab	Not assigned	Stop before conception Women of childbearing potential should use contraception while receiving treatment and for 6 months after the last infusion	Contraindicated	Contraindicated (excreted in the milk of ocrelizumab-treated monkeys but no data in humans)	Humanised monoclonal IgG antibody targeted against $CD20^+$ B cells Crosses placental barrier Very limited data – it is too early to tell – only approved by NICE this autumn with a warning against pregnancies[59]

FDA = US Food and Drug Administration; NICE = National Institute for Health and Care Excellence; SGA = small-for-gestational-age.

discussed, because some DMTs are known to pose risks to the newborn. It is also important to discuss the risk of stopping DMTs during pre-conception counselling with the woman. The fact that MS is not a hereditary disease and that the risk of having children who may develop the disease is very small should be reiterated during these consultations.[2,6] Women should be reassured that the risk of miscarriage, congenital malformation and perinatal mortality is not affected by MS per se. Women should be encouraged and supported to stop smoking because – in addition to its deleterious effect in pregnancy – cigarette smoking increases the risk of disease progression.[60]

Management of MS during pregnancy

Antenatal

Although, overall, pregnancies in women with MS run smoothly, it is important that they are managed in a multidisciplinary setting involving a neurologist with an interest in MS and pregnancy, an MS specialist nurse, an obstetrician with expertise in MS, a general practitioner (GP) and a community midwife. This will help to ensure that women are given the correct advice.

As pregnancy-related symptoms mimic MS exacerbations, extra vigilance is needed to assess these symptoms, as

Box 2. Summary of US Food and Drug Administration categories for drug safety during pregnancy

A: Controlled studies in animals and women fail to show fetal risk

B: Either animal studies show no risk and no data in women, or animal studies show an adverse effect that has not been confirmed in controlled studies of women in their first trimester

C: No controlled studies available in women and either animal studies not done or done and showed an adverse effect

D: Evidence of risk to the fetus but benefits may still outweigh this risk

X: Evidence of risk to the fetus and drug contraindicated in pregnancy

mentioned previously. Simple measures such as taking frequent rest and avoiding stress may be helpful for women with fatigue. A small dose of amitriptyline may be used to help with neurogenic pain, and diazepam can improve spasticity to some extent. Women with bladder symptoms and neurogenic bladder must have monthly midstream urine samples taken because of the increased risk of UTI in this cohort. Neurogenic bladder symptoms may worsen, with an increased need for intermittent self-catheterisation during pregnancy. Adequate hydration, a high-fibre diet and occasional use of laxatives can be considered in women who experience constipation. Consider thromboprophylaxis with compression stockings and low molecular weight heparin in women who have reduced mobility or who are wheelchair-bound and have additional risk factors;[61] these patients should also be warned against falls and may need increased physiotherapy. Anaesthetist review enables women to discuss pain relief options during labour and delivery. It is safe to use pethidine, nitrous oxide, a transcutaneous electrical nerve stimulation machine and regional anaesthesia during labour. Although there are theoretical concerns about the use of spinal anaesthesia, to date, no studies have found any detrimental effects of exposing the demyelinated spinal cord to the neurotoxic effects of local anaesthesia.[62,63] Fetal scan surveillance in the third trimester should be considered, given the increased risk of small-for-gestational-age infants in these women.[64]

Relapse during pregnancy is more likely to occur during the first and second trimesters. Use of magnetic resonance imaging (MRI) to confirm a relapse and exclude other pathologies is safe in all trimesters of pregnancy, but it is not often deemed necessary. However, MRI with gadolinium contrast should be avoided during pregnancy.[65] Management of acute flare-up usually involves oral or intravenously administered corticosteroids. This is safe during pregnancy and breastfeeding.[66] Vigilance is required regarding maternal hypertension and gestational diabetes with repeated courses of steroids in pregnancy. Fetal growth scans during the third trimester are also advised. It is very uncommon for women with MS to be given steroids (prednisolone equivalence of greater than 5 mg) for more than 4 weeks before giving birth, but they will need additional oral doses or parenteral hydrocortisone during delivery and in the immediate postpartum period to lower the risk of acute adrenal crisis.[67]

Labour and delivery

Obstetric indications will guide the timing and mode of delivery in women with MS. Vaginal delivery is considered safe; however, planned caesarean section may be considered in women with severe neurological problems. Women with higher EDSS scores are more likely to require induction of labour. Ensure the bladder is emptied periodically during labour, and it is advisable to use an indwelling urinary catheter with epidural anaesthesia. Increased fatigue and maternal exhaustion may warrant assisted delivery.

Postpartum and breastfeeding

It is recommended that the MS team formulates a postnatal plan for women with MS in the late third trimester. This plan should include vigilance for disease flare-ups, advice regarding drug treatments and their implications on breastfeeding, MS team contact numbers and follow-up appointments. A written copy should be made available to the woman, her GP and the obstetric team.

Women should be encouraged to breastfeed because of the benefits to babies, although the full extent of the benefit of exclusive breastfeeding in MS remains uncertain. However, breastfeeding is contraindicated when they restart on a DMT in the immediate postpartum period. Patients with very active disease prior to pregnancy usually restart their MS treatment immediately after delivery and choose not to breastfeed. Women must be reassured that breastfeeding is safe during steroid therapy. The British National Formulary advises to breastfeed 4 hours post-administration to minimise infant exposure.

Effective contraception is necessary to prevent unintended pregnancies in women with MS, especially during active disease, or if taking immunosuppressants for disease control because many of them are teratogenic. Based on the current evidence, most contraceptive methods are safe to take for women with MS.[68] It is important to consider the woman's level of disability, mobility and medication use when choosing the best contraceptive choice.

MS and assisted reproductive techniques

Several studies have shown that the rate of relapse is considerably higher following assisted reproductive techniques (ART),[69–71] and is significantly higher after unsuccessful attempts and following GnRH agonist protocols. The increased relapse rate tends to occur 3 months following ART. Correale et al.[70] prospectively followed 16 patients before and during an ART cycle. A seven-fold

increase in the risk of MS exacerbation was found, as well as a nine-fold increase in the risk of enhanced disease activity on MRI. Several factors contributed to the increased relapse rate, such as immunological changes during ART, with increased levels of pro-inflammatory cytokines and increased migration of immune cells through the blood brain barrier, stress and discontinuation of DMTs prior to ART.

Conclusion

Pre-pregnancy counselling and careful planning will allow women with MS to have a favourable pregnancy outcome. Women with MS should be reassured that pregnancy does not appear to be harmful overall – and may even be beneficial. For most patients with MS, pregnancy outcome is not significantly different from that of the general population, though some precautions may be required in patients with advanced MS. Given the potential benefits, breastfeeding should be encouraged during the postpartum period, but women should be counselled that DMTs may need to be commenced in the event of postpartum relapse. Although there is an increase in the relapse rate with ART, it is not contraindicated in women with MS.

Disclosure of interests

PK and DK have no conflicts of interest. NE served on scientific advisory boards for Merck, Biogen, Roche and Novartis and has received conference hospitality from Biogen and Teva.

Contribution to authorship

PK contributed to literature searches and drafted the article based on available evidence. DK and NE reviewed the manuscript and provided their comments. All authors read and approved the final version of the manuscript.

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