Pregnancy and multiple sclerosis

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Summary: The relapse rate of multiple sclerosis (MS) is typically reduced during late pregnancy but increases in the postpartum period. The reasons for the increased postpartum activity are not entirely clear, but factors such as the abrupt decrease in oestrogen levels immediately after the delivery and the loss of the immunosuppressive state of pregnancy are likely of importance. There is a general view that MS does not affect the course or outcome of pregnancy.

Keywords: multiple sclerosis, pregnancy, immunosuppression

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory disease in which the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms.¹ A person with MS can suffer almost any neurological symptom or sign, including changes in sensation such as loss of sensitivity/ numbness (hypoesthesia), tingling/pricking (paraesthesia), muscle weakness, clonus, muscle spasms or difficulty in moving; difficulties with coordination and balance (ataxia); problems in speech (dysarthria) or swallowing (dysphagia), visual problems (nystagmus, diplopia), fatigue, acute or chronic pain, bladder and bowel difficulties, and cognitive symptoms.¹ The most commonly used diagnostic tools are neuroimaging and analysis of cerebrospinal fluid. Magnetic resonance imaging (MRI) of the brain and spine shows areas of demyelination (lesions or plaques). Gadolinium can be administered intravenously as a contrast to highlight active plaques and, by elimination, demonstrate the existence of historical lesions not associated with symptoms at the moment of the evaluation.²

MS is the most common disabling central nervous system disease of young adults with a prevalence in the Western world of approximately one per 1000. About 80% of people with MS are diagnosed between the ages of 20 and 45 and, in adults, the female-to-male ratio is about 2.5 to 1. Hence, the majority of individuals obtaining the diagnosis of MS are women of child-bearing age.³ They are naturally concerned as to how a pregnancy will affect their disease, how the disease might modify the outcome of the pregnancy and influence the developing child, and how the medication they are using may affect the child.

EFFECTS OF PREGNANCY ON MS RELAPSES

Pregnancy is typically a stabilizing period in the clinical course of MS. During the third trimester the MS relapse rate can be

70% lower when compared with the time before pregnancy, but aggravation of the disease is commonly seen after delivery (Table 1).

Clinical data

Several early retrospective studies suggested that pregnancy has a beneficial effect on the clinical course of MS,^{4,5} but this view was not shared by all investigators.^{6,7} Uncertainty about how to advise young women with MS on their family planning was perhaps resolved after the publication of the pregnancy and multiple sclerosis (the PRIMS study).⁸ In the largest prospective study so far to evaluate the effect of pregnancy on the clinical activity of MS, Confavreux *et al.* followed 254 women with MS through 269 pregnancies. The study was conducted as a multi-centre study in 12 European countries. The enrolment was performed between four and 36 gestational weeks, and follow-up was continued for one year after the delivery. Data were collected on relapse frequency and disability. During the year prior to pregnancy 164 relapses occurred among the 227 women who were followed up for the entire observation period, reflecting an annual relapse rate of 0.7. During the pregnancy the relapse frequency steadily declined and reached the minimum annual relapse rate of 0.2 during the third trimester of pregnancy (meaning that during the third trimester only 12 of 225 women [=5%] experienced a relapse). In the three months following the delivery, the number of relapses increased dramatically to 68 of 222 women (=31%; annual mean relapse rate 1.2, $P < 0.001$ versus relapse rate during the year preceding pregnancy). Women with greater disease activity in the year before pregnancy and during pregnancy and a high level of physical disability have a higher risk of relapse in the three months postpartum.⁹ A similar pattern of lack of active inflammation during pregnancy and an increase in signs of inflammation during the postpartum phase has been observed in studies using serial MRI.^{10,11}

Immunological background for relapses

Successful pregnancy depends on the ability of the maternal immune system to tolerate a genetically incompatible fetomaternal unit. One of the important adaptations leading to

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Table 1 Pregnancy-associated factors influencing multiple sclerosis relapse rate

Factors associated with an increased number of relapses
Postpartum period
Drop in E2 (oestradiol) and E3 (oestriol) serum levels
Infections
Pre-eclampsia?
Factors associated with a low number of relapses
Second and third trimester of pregnancy
High E2, E3 and progesterone levels
Breastfeeding

this immunotolerance is the shift, at implantation, of helper T-cell1 (Th1) dominance to Th2 dominance. Since successful pregnancy is a Th2-dominant immune state, it is not surprising that women with Th1-dominant immune diseases, such as MS and rheumatoid arthritis, improve during pregnancy.^{12–15} Placenta-derived hormones, oestrogens and progesterone can directly affect the function of the immune cells through oestrogen and progesterone-receptors. During the course of pregnancy, the placenta-derived oestriol (E3) levels increase many-fold (from 0.2 ng/mL before pregnancy up to 10 ng/mL during gestational weeks 35–37). Related to this, a dramatic decrease in MS relapse frequency is observed during the latter half of pregnancy. On the other hand, the abrupt decrease in oestrogen levels following delivery is associated with an increase in inflammatory activity, which in MS is observed both as an increase in the relapse rate and as an increased lesion load on the MRI.^{8,11}

It has been suggested that oestrogens exhibit dose-dependent biphasic effects on immune cells, whereby high oestrogen levels inhibit and low oestrogen levels facilitate cell-mediated immunity.¹⁶ This has been put forward as one explanation for the higher prevalence of autoimmune diseases among women (low oestrogen) and for improvement of the cell-mediated autoimmune diseases such as rheumatoid arthritis and MS during pregnancy (high oestrogen). Pauklin *et al.*¹⁷ recently showed that, acting through activation-induced deaminase, oestrogens could induce antibody-mediated autoimmunity; this could also contribute to the female-predominance of MS. It also fits well with the notion that during pregnancy, Th2-type antibody-mediated immune responses are beneficial for the outcome of pregnancy and thus prevalent.¹³ The anti-inflammatory effects of oestrogens are also well documented by *in vitro* studies, and oestrogens delay the onset of experimental autoimmune encephalomyelitis.^{18,19}

Medicinal oestriol reduces the number of inflammatory lesions on brain MRI of MS patients.²⁰ A small group of female MS patients were given oestriol at a dose corresponding to the late pregnancy physiological concentration (8 mg/day). This led to a reduction in the number of active lesions on the brain MRI, and alterations were also measured in systemic cytokine levels. The drug was well tolerated, and hence the results from this small preliminary study were considered very promising. A larger oestriol study in the treatment of relapsing remitting MS is ongoing in the USA.

MRI during and after pregnancy

MRI imaging is widely used during pregnancy, either for fetal or for maternal diagnostics. In most cases, because of theoretical concerns, MRIs are not performed during the first trimester. A

rise in body temperature, especially locally in the uterus, and acoustic noise exposure have been mentioned as potential theoretical risks. In animals, gadolinium has not been shown to be a teratogen but safety data in humans concerning gadolinium administration during pregnancy are lacking. Hence use of gadolinium is usually avoided during pregnancy.

Paavilainen *et al.*¹¹ reported the first MRI study of an MS cohort (of 28 study subjects), which addressed disease activity during pregnancy and the postpartum period. There was a significant increase in the number of T2-lesions ($P = 0.0009$) and diffusion weighted imaging lesions ($P = 0.0098$) as well as in the total lesion load measured from FLAIR images ($P = 0.0126$) in scans performed after delivery when compared with the scans performed during pregnancy. No alteration was observed in the number of T1-lesions ($P = 0.375$). Fourteen of the patients (50%) showed T2-activity (i.e. the scans contained one or more new, or enlarging, lesions) in at least one of their postpartum scans (mean 3.7 active lesions, range 1–14). The majority of the active postpartum scans (9/14) were performed within five weeks of delivery. This indicates that MS disease activation commonly takes place at a very early stage after the delivery. Furthermore, active lesions were also observed in two scans performed at 35–37 gestational weeks, which suggests that alterations may already be taking place in the mothers' immune system during very late pregnancy in preparation for the delivery of the fetus. Interestingly, blood oestriol concentration begins to decline after 35 gestational weeks, reflecting the dysfunction of the ageing placenta. Consequently, the loss of high oestriol concentrations might lead to an increase in MS activity in certain patients. In some cases, clinical MS disease activity has also been described shortly before the delivery.²¹ In conclusion, during the six-month postpartum period, 21 of 28 (75%) patients demonstrated MS disease activity either by a clinical MS relapse or by a T2 activity on the MRI scans.¹¹

PREGNANCY OUTCOME IN MS PATIENTS

Two larger, retrospective register-based studies and a few prospective studies with smaller patient numbers have addressed the question of pregnancy outcome among MS patients.^{21–23}

Presently, there is no evidence that MS patients are more susceptible to pregnancy or delivery complications, such as ectopic pregnancy, pre-eclampsia, gestational diabetes mellitus, prolonged labour or miscarriage than women in general, nor are their infants more likely to be delivered preterm, to be of low birth weight, have malformations or experience an early death. Fertility problems or congenital abnormalities are also uncommon in women with MS. In a register-based study on MS births between 1967 and 2002 the singleton children born to MS mothers had on average 123 g lower birth weight when compared with infants of healthy control mothers; a difference stated as statistically significant ($P < 0.001$).²³ Based on the same report, mothers with MS needed operative delivery more often than healthy mothers, which might be due to MS-related symptoms such as neuromuscular perineal weakness and spasticity in addition to fatigue and exhaustion.

Delivery of MS mothers

The possibility of the need for an operative delivery should be taken into account when planning a delivery of a mother with MS but, overall, the decision for an elective caesarean section

should be made based on current obstetric criteria.²¹ The mother's functional status should of course always be taken into account: a mother with significant functional disability will be more likely to encounter problems associated with fatigue and exhaustion during the second stage of delivery.

Anaesthesia during delivery

Epidural anaesthesia during delivery was not associated with increased risk of postpartum flares or disability in women with MS in the PRIMS study.⁸ On the other hand, concerns have been raised about spinal anaesthesia. It has been suggested that spinal anaesthesia may be the explanation for postoperative relapses. The theoretical basis for the concerns is that the local anaesthetics might have a direct toxic effect on the demyelinated axons,²⁴ but there are no real clinical data to support these concerns.

TREATMENT OF MS DURING PREGNANCY AND LACTATION

Treatment during pregnancy

With the increasing incidence of MS in women and the more frequent use of disease modifying therapies (DMT), issues surrounding DMTs and pregnancy are a regular subject of discussion with regard to optimal management. Current recommendations are to withdraw DMTs prior to conception, leaving patients exposed to an uncertain period of untreated disease. However, attitudes to a washout period are becoming more relaxed as more information has been gathered on the effects of DMTs on pregnancy outcome, and many experts now recommend cessation of DMTs at the time point when the patient realizes that she is pregnant.

The main DMTs used in MS are interferon-beta 1a/b, glatiramer acetate, mitoxantrone, azathioprine and natalizumab. In a recent retrospective study in Spain, 38.6% of MS mothers on interferon-beta therapy did not discontinue the treatment until during the first trimester of pregnancy.²⁵ Hence, a significant proportion of MS mothers may be exposed to DMT during pregnancy. Interferon-beta has been associated with an increased risk of spontaneous miscarriage and lower birth weight of the new-born in one small prospective study,²⁶ but other investigators have considered the drug safe in terms of pregnancy outcome.^{25,27-29} This has been confirmed recently by a Swedish study. In cases for which exposure duration was available ($n = 231$), mean time of fetal exposure to subcutaneous interferon beta-1a before treatment discontinuation was 28 days; most pregnancies (199/231; 86.1%) were exposed for ≤ 45 days. To avoid bias, only outcomes for prospective data ($n = 425$) in pregnancies exposed to interferon beta-1a *in utero* were analysed further. Of these, 324 (76.2%) resulted in normal live births and four (0.9%) in live births with congenital anomalies (3 [0.7%] were 'major'). Four (0.9%) pregnancies resulted in stillbirths (1 [0.2%] with fetal defects). There were 5 (1.2%) ectopic pregnancies, 49 (11.5%) spontaneous miscarriages and 39 (9.2%) elective terminations.³⁰ These frequencies do not differ from those in the corresponding general population. Experience from many hundreds of pregnancies with (mostly first trimester) exposure to interferon-beta is sufficient to conclude that interferon therapy seems quite safe during pregnancy, and the medication can be used until the pregnancy

is confirmed. As pregnancy is normally a stabilizing period for MS, treatment of MS during pregnancy is rarely necessary.

There are many reports on the use of glatiramer acetate (GA) during pregnancy (e.g. 100 exposures from the Swedish Birth Registry) and so far there are no signs of increased risk of fetal malformations. In a prospective study 14 pregnancies in 13 women resulted in 13 live births, of which nine were exposed to GA throughout pregnancy. There were no birth defects and no relapses occurred during pregnancy in those who continued GA treatment.³¹

There are also numerous reports of azathioprine use during pregnancy.³² Azathioprine and its main metabolite, 6-mercaptopurine, cross the placenta, but the plasma concentrations in the fetus are very low. There is one recent report on two successful pregnancies on natalizumab, and in one report on the use of mitoxantrone, the pregnancy resulted in the delivery of a growth-restricted baby.^{33,34}

Taken together, the information on pregnancy outcomes for babies exposed to DMTs is increasing, but the study samples are still small. Even though these drugs do not appear to cause any major fetal malformations it is uncertain how they might affect the developing immune system of the fetus. In addition, the natural course of MS during pregnancy, i.e. the pregnancy-associated low annual relapse rate, makes the necessity of DMTs questionable during pregnancy. Despite discontinuation of the DMT before or in the beginning of pregnancy, the mothers rarely experience disabling relapses during the course of pregnancy. If a mother does experience a disabling relapse during pregnancy, she could be safely treated with a course of intravenous immunoglobulin (IVIg), or with high-dose methylprednisolone.

Breastfeeding and MS

The prevalence of breastfeeding was very high (90%) in a cohort of German MS mothers and in a cohort of Finnish MS mothers.^{35,36} This is in stark contrast to a South-European MS population, where only 28.6% of mothers chose nursing.²⁵ Breastfeeding is considered beneficial for the mother-infant relationship, and it reduces the incidence of infections and allergies experienced by the infant.³⁷ Moreover, both in the PRIMS study and a more recent small study performed in California, the MS patients who breast-fed their children had a lower relapse rate than women who did not breast-feed.^{8,38} This probably does not reflect a positive effect of breastfeeding on MS activity; it rather implies that the mothers with active disease chose DMT instead of breastfeeding.³⁶

Treatment of postpartum relapse

The postpartum period is a more challenging time regarding controlling the disease activity, especially in areas of high breastfeeding prevalence. Mothers with MS are interested in reducing the probability of experiencing postpartum relapses in order to best manage with their child, but treatment with DMTs is not recommended during nursing. One therapeutic option is IVIg, which is safe to use during breastfeeding, and which has been suggested to reduce disease activity in MS,³⁹ although in a later study no benefit could be demonstrated.⁴⁰ A retrospective study however suggested that IVIg may be effective in preventing postpartum relapses.⁴¹ Recently, a large (173 patients) multicentre, randomized double-blind

clinical trial compared two different doses of IVIg treatment during the postpartum period, but no difference was observed between the two dosing regimens. A randomized, placebo-controlled study on the effect of IVIg in preventing postpartum relapses is, unfortunately, still lacking. Taken together, prophylactic treatment with IVIg could be given in selected cases, such as for those mothers with a high pre-pregnancy disability and/or high relapse rate before and/or during pregnancy.

CONCLUSIONS

MS relapses are normally greatly reduced during the latter half of pregnancy, but after the delivery the disease often activates. Discontinuation of disease-modifying treatment is recommended at the latest when the pregnancy is confirmed. Breastfeeding is considered beneficial for the infant, but disease-modifying treatment is not recommended while breastfeeding. The mothers with highest disability and highest relapse rate are most likely to experience postpartum relapses, which should be taken into account when planning treatment after the delivery. The outcome of pregnancies of MS patients is normally good.³⁶

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