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FIGHTING MULTIPLE SCLEROSIS

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NEWSLETTER

Pregnancy and multiple sclerosis: it's not incompatible

This issue mainly deals with pregnancy management, breastfeeding and postpartum in MS patients. This disease actually affects three times more women than men and generally begins between the ages of 25 and 35, i.e. during the procreative years. As a result, it very frequently affects family planning and raises many questions among the people concerned.

One of the major issues is whether to continue or suspend a background treatment during pregnancy and the postpartum period, and the solution very much depends on the medication used, which may in some cases be continued during pregnancy and breastfeeding, and in other cases has to be discontinued prior to conception or as soon as there has been a positive pregnancy test. In yet other cases, after being discontinued during pregnancy, treatment must be resumed immediately after childbirth to prevent postpartum flare-ups. Professor Brigitte Capron supplies a summary of this complex issue, with the advantages and drawbacks of all medications currently used to treat MS.

Dr Barbara Willekens has also contributed a reassuring article showing that pregnancy does not adversely affect the progress of MS in the long term. **The disease does not significantly worsen or progress faster in women who have been pregnant, whether before or after the appearance of MS.**

In the huge majority of cases, therefore, there is no neurological contraindication to pregnancy in MS patients. An excellent American study analysed the proportion of pregnant women with or without MS between 2006 and 2015, and it is comforting to see that this proportion increased from 7.91% to 9.47% in MS patients and decreased from 8.83% to 7.75% in MS-free women. With remarkable resilience, MS patients were determined to live normal lives and start a family, to the point that they carried their pregnancies to term more often than the control population. This is also a sign that our medications are increasingly effective in terms of reducing disability and enabling self-reliance.

Prof. Dr. Christian Sindic

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Planning a pregnancy: managing treatments

Further to several decades of mistaken beliefs concerning the risks posed by pregnancy in female MS patients, data from large-scale prospective studies such as PRIMS (1998) have made it possible to establish the facts and advise such patients on a solid scientific basis.

> *“Nowadays, it is clearly stablished that MS patients should not established discouraged from getting pregnant.*

Nevertheless, the postpartum period remains critical in terms of the resurgence of disease activity, which returns to its pre-conception levels and may therefore be fairly high in the case of forms very active prior to pregnancy. It is consequently important that this period be covered with effective therapy, an appropriate lifestyle and adequate periods of rest.

We therefore suggest that family planning be discussed at an early stage with MS patients, especially in connection with the choice of background treatment, as a number of them are contraindicated during pregnancy and therefore need to be stopped, hence the importance of discussing the patients' wish to become pregnant as soon as the first treatment is set up, and of bringing up the subject regularly (at least each time medication is changed). Such pre-conception talks are essential if the patient is to be able to make informed choices.

In the event of a pregnancy, should a treatment need to be stopped, it is essential to do so at the right time. In such cases, a patient may find herself going without treatment for almost or even over a year. The decision to cover the pregnancy with a compatible background treatment chiefly depends on the risk of a flare-up during the pregnancy – especially in the case of the very active forms – but also on the increase of that risk postpartum. It so happens that few treatments are immediately effective in such a way as to cover this crucial time as soon as they are administered once more.

Generally, it is best to plan a pregnancy when MS has been perfectly stabilised, ideally for a period of 2 years, and for at least 12 months. In this case, when the background treatment needs to be suspended, this will at least be done during a period of stability. As well as clinical examination, an analysis of a brain MRI during the year prior to the pregnancy will supply additional information concerning the absence of new or active lesions, to confirm the absence of disease activity.

However, it frequently happens that pregnancies are not planned, in which case it is not easy to follow the advice supplied hereunder. There is no reason to panic, though. In such situations, the current treatment should be stopped immediately (unless it has been confirmed to be compatible with pregnancy) and the patient should get in touch with her neurologist, as well as her gynaecologist-obstetrician, to set up close obstetrical monitoring (including, for instance, repeated morphology ultrasounds). Finally, the fact that the pregnancy was begun under medication should be notified to the pharmacovigilance centre to ensure monitoring of its progress and outcome. If a register of pregnancies has been opened specifically for the treatment in question, it should also be notified and consulted.

The decision whether to pursue a background treatment should be taken by balancing the risk to the foetus against the risk that the mother's MS may worsen.

This paper will discuss the maintenance or interruption of each of the background treatments, mainly in women, should they express a wish to have a baby – at the planning stage, as it were. This includes the right time to stop using contraception, the maintenance or interruption of the treatments, the resumption of the treatment postpartum, and if applicable compatibility with breastfeeding.

The following recommendations have been issued by expert groups and are known as “international guidelines”. They are based on drug information leaflets, the drugs' FDA classification, their molecular characteristics, the real-life data, etc.

First-line treatments

Beta interferons and glatiramer acetate

Neither of these drugs need be stopped prior to contraception and both can be taken throughout pregnancy and breastfeeding.

Dimethyl fumarate

Dimethyl-fumarate treatment can be continued until pregnancy is confirmed by a positive test. It should then be stopped. This medication should not be taken when breastfeeding and its resumption should be postponed until breastfeeding has ended.

Teriflunomide

This treatment is contraindicated during pregnancy. However, it is not enough to cease taking it as it persists in the blood for

several weeks (if not months). Effective contraception should therefore continue to be used after discontinuing teriflunomide and during the period of accelerated drug elimination by administration of cholestyramine 3x4g/day for 11 days. This lowers the blood level to less than 0.02 mg/l and contraception may then be discontinued. This treatment should also not be used during breastfeeding.

Ponesimod, siponimod and ozanimod

These three drugs are related to fingolimod and should not be used during pregnancy. They are also contraindicated during breastfeeding. Contraception should be continued for 7 days after the last dose of ponesimod, 10 days after the last dose of siponimod and 3 months after stopping ozanimod, in accordance with the half-lives of each of these medications. Since there is no officially identified risk of rebound as in the case of fingolimod, the replacement of these treatments with another in the event of a planned pregnancy may be discussed case by case with the patient's neurologist, and depends among others on disease activity during the past 24 months.

Second-line treatments

Fingolimod

Fingolimod must not be used during pregnancy. Moreover, the patient should continue to use effective contraception for 2 months after the treatment has been discontinued. Finally, given the risk of a rebound in the inflammatory activity of the disease (in the form of a severe flare-up or increased lesional load), a switch to another background treatment compatible with pregnancy is highly recommended (to be discussed with the patient's neurologist). Breastfeeding is also contraindicated when taking this drug.

Natalizumab

Treatment with natalizumab may be continued until pregnancy is confirmed. Thereafter, in view of the risk of relapses when treatment is stopped (especially in the case of very active MS prior to initiation of treatment), it may be necessary to continue treatment during the first 2 trimesters of pregnancy (up to 32-34 weeks) and resume it as soon as possible after birth, in order to limit the interruption of the treatment to 8-12 weeks. Continuation or initiation of natalizumab during the third trimester should be discussed according to the severity of the disease (severe recent flare-up, for instance) and weighed against the potential haematological side effects for the foetus.

It is advisable to space out doses (6 weeks between administrations instead of 4) in order to reduce drug exposure.

Breastfeeding may be considered in the event of treatment with natalizumab, as concentrations of this drug in milk are very low. Moreover, it will be largely destroyed in the infant's gastrointestinal tract.

Ocrelizumab

It is recommended that ocrelizumab not be used during pregnancy. French experts recommend waiting at least 2 months between the last intravenous infusion and the discontinuation of contraception, while British experts advise that contraception may be discontinued immediately after the last infusion. This is because there is no significant transplacental transfer of this antibody during the first trimester of pregnancy.

If the patient is not pregnant 6 months after her last treatment, an extension of the dose interval (from 6 to 9-12 months) may be considered in order to allow a longer period for conception. Exceptionally, this drug may be given during pregnancy if this is required to control the disease and no other satisfactory alternative can be considered.

Treatment may be resumed during breastfeeding, as transmission via breast milk is very slight, as in the case of other monoclonal antibodies.

Ofatumumab

This drug is contraindicated during pregnancy and contraception should be used until the treatment is stopped.

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However, it can be given during breastfeeding, as the large size of the molecule means that little finds its way into the milk and this type of molecule is also partly destroyed in the infant's gastro-intestinal tract.

Cladribine

Cladribine is contraindicated during pregnancy. It is recommended that effective contraception be maintained up to 6 months after the last dose of medication. This recommendation also applies to **male MS patients who wish to have children**. However, this immune-reconstitution treatment does provide a therapeutic window for conception in view of its administration, which is intermittent and spread over 5 weeks per year for 2 consecutive years.

Breastfeeding is contraindicated in patients treated with cladribine while taking the drug and for up to 1 week after the last dose.

Alemtuzumab

It is recommended that alemtuzumab not be used during pregnancy. However, as this treatment is limited to patients in whom the disease is highly active, it can be assumed that pregnancy was not on the agenda when this treatment was chosen. Should this be the case, its cyclical treatment schedule (5 days of IV treatment in the first year, followed by 3 days of IV treatment in the second year) makes it easy to find a window of opportunity for conception: effective contraception is recommended for up to 4 months after the last course of treatment, and can then be discontinued if the patient wishes to become pregnant.

A monthly assessment of thyroid function is recommended if the last treatment with alemtuzumab was given less than 4 years previously, in order to detect autoimmune thyroid disease, which is frequently reported as a medium- and long-term side effect of this treatment.

According to the European Medicines Agency, it is also contraindicated during breastfeeding for up to 4 months after administration. However, if the same principle is applied concerning passage into breast milk and destruction in the infant gastrointestinal tract as in the case of the other monoclonal antibodies, it could probably be started immediately.

Despite the guidelines supplied in the scientific literature during the past few years to aid neurologists in their decision-making, many of them are reluctant to continue a background treatment during pregnancy and breastfeeding, and clinical practice in this area varies widely.

The purpose of this summary is to supply the clearest possible overview of the management of MS background treatments in the event of pregnancy and breastfeeding. Of course, the severity of the disease and the patients' wishes (customised treatment) also need to be taken into account.

Finally, these recommendations are not definitive and may change over time, depending on the real-life data collected in pregnancy registers worldwide for each drug (planned and unplanned pregnancies with permanent or temporary exposure to a treatment). Hence the importance of recording all pregnancies that occur after exposure to background treatments in pharmacovigilance registers or in observational studies.

Prof. Brigitte Capron, CHU Marie Curie, Charleroi

The references of all the studies cited are available on request from the Belgian Charcot Foundation.

Impact of pregnancy on the course of MS

Since the seminal study on pregnancy-related relapse rate in MS by the late Christian Confavreux and the PRIMS study group was published in 1998, several other studies on the impact of pregnancy on the disease on the course of MS have been carried out. The conclusions of these contemporary cohort studies have not changed significantly since then.

It has been well established that **the relapse rate declines in the third pregnancy trimester, but increases during the first three months postpartum before returning to the pre-pregnancy rate**. In 2004 risk factors for postpartum relapse were identified in this PRIMS cohort. Disease activity in the year before pregnancy and during pregnancy were identified as risk factors for an increased postpartum relapse risk. However, despite the increased risk, almost three quarters of the women did not experience a clinical relapse postpartum.

A recently conducted meta-analysis included 11 cohort studies including 2739 pregnancies, in order to assess the association between pregnancy and MS relapse activity. A significantly increased relapse rate was demonstrated in the first 6 months postpartum in comparison with preconception rate. The incidence rate ratio (IRR) almost doubled in the first 3 months postpartum (1.87, 95% CI 1.40 to 2.50). Analysis of possible risk factors suggested that pre-conceptional Disease Modifying Therapies (DMTs) (IRR for highly effective DMTs 2.76, 95% CI 1.34 to 5.69) and exclusive breast feeding (risk ratio 0.39, 95% CI 0.18 to 0.86) significantly influenced postpartum relapse risk.

Early studies did not include brain MRI as outcome. A recent study performed in the USA reported a significant association between active inflammation on MRI and disease activity. Of seventy pregnancies with paired brain MRIs available, new T2 and/or Gd+ lesions postpartum occurred in 53%, compared with 32% pre-pregnancy ($p < 0.001$). Postpartum clinical relapses were associated with Gd+ lesions ($p < 0.001$). However, in 31% of patients without clinical disease activity postpartum, brain MRIs showed new T2 and/or Gd+ lesions.

We can thus conclude that the higher postpartum relapse risk and increase in inflammatory disease activity on MRI has been clearly established. However, long-term effects of pregnancy on the disease on the course of MS remain more controversial. Indeed, earlier studies suggested a protective effect of pregnancy on MS, meaning that women who had at least one pregnancy demonstrated slower disability accumulation. However, these results have been challenged by recent studies.

> *“Reassuringly, pregnancy does not influence long-term disease progression.*

In the context of the Barcelona CIS (clinically isolated syndrome) cohort, a cross-sectional survey was conducted to collect reproductive information of 501 female participants.

In this cohort, menarche, pregnancies, and breastfeeding did not substantially modify the risk of developing clinically definite multiple sclerosis or disability accrual using a multivariable and time-dependent approach. The finding that pregnancy does not influence long-term disability accumulation was confirmed in the nationwide Danish MS registry, in which 425 parous women were compared with 840 nulliparous women. Time to reach EDSS 4 or 6 was not influenced by pregnancy.

Contemporaneous cohort studies confirm the historical findings of increased relapse risk in the postpartum period. Reassuringly, pregnancy does not influence long term disease progression.

This information can help to counsel women with MS who have a pregnancy wish.

Dr. Barbara Willekens, UZA, Antwerp

YOUR BEQUEST WILL ENABLE RESEARCHERS TO GO FURTHER AND FASTER

Thinking about your will is never easy. We'd all like to have a say after we go and decide for ourselves what will happen to our estate.

This is what Jacqueline told us: "*With time, I've come to have a different take on life. I'm 75, I have grandchildren, and I'd like them to have the best possible future. My sister has MS and the whole family feels strongly about the issue. So obviously, when I began to consider where to leave my estate, I included a legacy to the Belgian Charcot Foundation, to pay for MS research and help beat the disease. That way, I'll carry on supporting the Foundation as I've been doing for several years now.*" Jacqueline B.

Why choose to make a donation in your will to the Belgian Charcot Foundation?

- because multiple sclerosis is still incurable and very often evolves into a disability and disrupts the lives of thousands of people
- because all the efforts we can make now bring us closer to the solutions: stopping the disease, repairing its damage and one day beating it completely
- because we commit ourselves to invest your donation completely in MS research.

Do you have any questions?
We will answer you in complete discretion.

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