

Family planning, pregnancy and breastfeeding in multiple sclerosis

Multiple sclerosis often affects women of childbearing age. The availability of more effective immunomodulatory therapy may increase the number of afflicted women wanting to fulfil their desire to have children. The purpose of this article is to provide an up-to-date review of medical issues and dilemmas related to family planning and pregnancy in multiple sclerosis.

Many women with multiple sclerosis wish to have children. However, they are often unsure whether the disease and its therapy will affect their chances of doing so, and whether there will be implications for their own health and that of the child. This article aims to address these issues and to highlight the importance of considering factors related to family planning and pregnancy when choosing therapy.

The article is based on a discretionary selection of articles indexed in PubMed, summaries of product characteristics (SPCs), relevant databases and our own clinical experience.

One of the first things that individuals diagnosed with multiple sclerosis wish to know is how much risk their children have of developing the disease and whether anything can be done to prevent this. If only one parent has the disease, this risk is still relatively low at 2–3 %, which is about ten times greater than the general population risk (1). The risk increases if multiple family members have the disease, and is approximately 20 % if both parents are affected.

Smoking and low vitamin D levels are associated with increased prevalence of multiple sclerosis in the general population (2). A Finnish study showed that a child's risk of developing the disease is almost doubled if the mother has low serum levels of vitamin D (3), but whether vitamin supplements reduce the risk accordingly is unknown.

Fertility

Neither multiple sclerosis itself nor commonly used immunomodulatory drugs appreciably reduce fertility, but women with the disease nevertheless have somewhat fewer children than other women (4). Sexual dysfunction occurs in 30–70 % (4) and is probably underreported and undertreated. Bladder and bowel disorders, erectile dysfunction, fatigue disorders, loss of tactile sensation, decreased libido and decreased ability to achieve orgasm may lead to reduced sexual activity in people with the disease (4).

Although women with multiple sclerosis do not require longer than others to conceive (5), in vitro fertilisation appears to be used relatively frequently (6). The medications involved – gonadotropin-releasing hormone agonists (GnRH agonists) – have immunological effects that could in principle trigger disease activity, and small observational studies support this possibility (6). The risk may be particularly high in women who have an aggressive form of the disease and who discontinue potent immunomodulatory therapy with natalizumab or fingolimod (7).

High-dose chemotherapy with autologous stem cell support is an experimental therapy that is used increasingly in multiple sclerosis, and which may reduce fertility. Cryopreservation of sperm is a simple procedure. Cryopreservation of ovarian tissue or unfertilised oocytes after GnRH stimulation is considered an experimental procedure of more uncertain benefit. As with assisted fertilisation, the GnRH stimulation has the potential to trigger disease activity (6). In our view, caution should be exercised in the use of such procedures prior to a stem cell transplant if the patient has discontinued her regular immunomodulatory therapy and is therefore particularly vulnerable to disease activity.

Contraception

Contraception should be discussed with patients of childbearing age, especially if opting for medicines with potentially teratogenic effects, such as fingolimod and teriflunomide (8).

Deep vein thrombosis is a rare complication of oral contraceptive use, and patients with spasticity and reduced mobility may in principle be at increased risk. Teriflunomide interacts with oral contraceptives to increase serum concentrations of ethinyl estradiol and levonorgestrel by approximately 50 % (9), which may in principle increase the risk of thrombosis.

There have been no other reports of any method of contraception having exacerbated

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the disease, or of additional adverse effects or interactions (8, 9). As a general rule patients may therefore use contraception as normal.

Immunomodulatory therapy

Several studies show a reduction in relapse rate towards the end of pregnancy and a transient increase in the first six months postpartum (6, 9). Previous studies found that pregnancy did not affect the long-term clinical course of multiple sclerosis (6, 9). This may no longer be the case, as discontinuation of modern potent immunomodulatory drugs can lead to greatly increased disease activity.

In accordance with the precautionary principle, standard practice has been to advise women to discontinue all immunomodulatory drugs before attempting to conceive, with a washout period determined by the drug's half-life (10). In our view, this focuses solely on the potential risk to the fetus – which for some drugs is probably minimal (11, 12) – and neglects the risks to the woman's health, which in some cases may be substantial (7, 13).

RELIS – a network of four regional medicines information and pharmacovigilance centres in Norway – has advised against consulting the Norwegian Pharmaceutical Product Compendium about the use of medications during pregnancy and breastfeeding, on the grounds that SPCs reflect legislation and the requirements of the medicines regulatory authorities more than medical considerations (14). Our recommendations therefore deviate in some cases from approved SPCs. Up to date and searchable information about the safety of drugs during pregnancy and breastfeeding can be obtained from the Australian Government Department Of Health's «Prescribing medicines in pregnancy» database and the National Institutes of Health (Lactmed and Developmental and Reproductive Toxicology database on Toxnet) (15, 16).

The effects of most immunomodulatory drugs will cease within a few weeks or months of treatment discontinuation (7, 17). In patients who were using natalizumab or fingolimod, disease activity may sometimes exceed pre-treatment levels (7, 13, 17). Rebound disease activity appears to be most pronounced with natalizumab (7) and may further increase the risk of active disease postpartum.

The average time required to conceive is about eight months (5), which means that many women who discontinue natalizumab therapy prior to a planned pregnancy may be exposed to increased disease activity before becoming pregnant. Glatiramer acetate and interferons do not seem to protect against increased disease activity following natali-

zumab cessation (14), and it is therefore usually inadvisable to switch to these drugs in advance of a planned pregnancy.

Natalizumab

Animal studies have not shown natalizumab to be teratogenic (6). In a recent American registry study of women with multiple sclerosis or Crohn's disease who had been exposed to natalizumab three months or less prior to pregnancy, major congenital malformations were reported in 16 of 316 live births (5.1 %), although there was no pattern suggesting a specific teratogenic effect (18).

The incidence of malformations was nevertheless higher than would have been expected from the incidence in a population-based American database (2.7 %), while the number of miscarriages was similar to that in the general population. The vast majority of patients in the study had discontinued natalizumab prior to or immediately after discovering that they were pregnant.

A German registry study with roughly 100 women who had been exposed to natalizumab during the first trimester showed no increase in the incidence of malformations (19). A small cohort study of women exposed to natalizumab in the last trimester showed no adverse effects beyond mild, transient haematological abnormalities in the infants (20).

Although the number of exposed human pregnancies is too small to allow definitive conclusions to be drawn, it has been suggested that patients with active disease prior to natalizumab initiation should be allowed to remain on the drug until they become pregnant, and in exceptional cases throughout all or part of the pregnancy (6). Extending the interval between infusions may then be considered in order to reduce fetal exposure. This does not seem to reduce therapeutic effectiveness (21). The benefits of treatment, which are substantial in women with aggressive disease, must in each case be weighed against the potential risk to the child.

Alemtuzumab and rituximab

Alemtuzumab and autologous stem cell transplantation are induction therapies that continue to act on the immune system long after the drugs concerned have been eliminated from the body (22). The woman can thus become pregnant after a washout period of a few months and will be protected during pregnancy and breastfeeding without the fetus or infant being exposed to drugs.

Alemtuzumab kills both T- and B-cells and its use poses a considerable risk of thyroiditis, with hyper- or hypothyroidism observed for several years after treatment (22). Metabolic status must therefore be monitored fre-

quently during pregnancy. Monoclonal antibodies targeting B-cells are effective against multiple sclerosis, without the same risk of thyroiditis.

Rituximab is not approved for use in multiple sclerosis, but is frequently used off-label for this purpose in Sweden (23). Another B-cell antibody – ocrelizumab – is expected to be approved in 2017 for the treatment of multiple sclerosis (22).

Beta interferon and glatiramer acetate

The long-established injectable preparations of beta interferon and glatiramer acetate provide moderate protection against disease activity and are still used by many women of childbearing age. There are at least 1,500 documented cases of interferon exposure during pregnancy, and at least 400 for glatiramer acetate (6). While this is a larger data set than for the other drugs, it is still relatively limited owing to the fact that most women discontinued treatment early in pregnancy.

These preparations are considered relatively safe for use during pregnancy (4, 6, 9), as prospective cohort studies have recently confirmed (24, 25). We recommend that these drugs can be used until the woman becomes pregnant and, on the basis of individual assessment, also throughout the pregnancy itself.

Somewhat paradoxically, the Norwegian Pharmaceutical Product Compendium states that the drug with the most favourable assessment from the Food and Drug Administration (FDA) (glatiramer acetate) cannot be used during pregnancy, but is open to the potential use of several agents with more unfavourable or uncertain profiles (natalizumab, dimethyl fumarate, interferons).

Teriflunomide, dimethyl fumarate and fingolimod

Orally administered medications have recently become available for multiple sclerosis. Two of these (teriflunomide and fingolimod) are teratogenic in animal studies, whereas this has not been observed for dimethyl fumarate (10).

Teriflunomide has a half-life of several months, and can take up to two years to be fully eliminated from the body unless accelerated elimination is used (26). The only published report on humans contains data on 70 cases of fetal exposure during pregnancy. Of these, 29 ended in induced abortion and 27 in a live birth, none with congenital malformations (27).

The FDA considers teriflunomide to have the most unfavourable and uncertain safety profile in pregnancy (10). Women using the drug who wish to become pregnant, or who become pregnant unintentionally, should

use accelerated elimination with activated charcoal or cholestyramine. Elimination should be confirmed via a blood test administered by the importer.

Data have been published on 66 pregnancies in which the fetus was exposed to fingolimod in utero (28). Five infants showed abnormal development, including one infant with acrania who died two days after birth. The numbers are too small to establish or rule out the possibility that fingolimod increases the incidence of congenital malformations (29), but they underscore the importance for women taking the drug to use effective contraception (30). Since a considerable proportion of pregnancies are unplanned, this issue should be taken seriously and discussed with all women of childbearing age when choosing a therapy.

With the possible exception of teriflunomide, where very little information is available in humans and preclinical studies show teratogenicity, the risk of harm to the fetus following exposure to immunomodulatory drugs is, in our view, so low that it is not in itself an indication for termination. The value of early ultrasound examination is uncertain.

Birth

A Norwegian study showed that infants born to women with multiple sclerosis had birthweights roughly 100 g lower on average than other infants, and were more frequently delivered by caesarean section (31).

Multiple sclerosis per se does not increase the risk of congenital malformations, and standard obstetric procedures can be followed (32).

Breastfeeding

The endocrine effects of breastfeeding may be beneficial for the immune system in multiple sclerosis. Some studies, though not all, suggest that breastfeeding protects against disease activity, and a meta-analysis concluded that the risk of postpartum relapse is almost twice as high in women who do not breastfeed (33). The potential protective effect appears to be greatest with exclusive breastfeeding (34).

However, it is not necessarily the case that breastfeeding reduces disease activity; another possibility is that mothers with little disease activity are more likely to succeed at breastfeeding. Since the risk of disease activity is high postpartum, it is generally advisable for women to resume immunomodulatory therapy within a week of giving birth. This is most important for women with a history of aggressive disease who were using fingolimod or natalizumab before pregnancy (10).

There are very limited data available on

the transfer of medicines into breast milk and any effects on the infant. The high molecular weights of glatiramer acetate and interferon probably limit their transfer into breast milk. Beta interferon was detected at very low concentrations in breast milk (35), corresponding to less than 0.01 % of the maternal dose. Both drugs are likely to be degraded in the infant's gastrointestinal tract. In our opinion they are therefore safe to use during breastfeeding, but some experts advise against this because they believe that safety has been inadequately studied (10).

The oral preparations fingolimod and teriflunomide are considered probably dangerous in view of their pharmacokinetic and pharmacodynamic profiles (36). Dimethyl fumarate also passes into breast milk and its use is therefore not recommended during breastfeeding.

Women treated with alemtuzumab before pregnancy can breastfeed freely, in our opinion, because the drug will long since have been eliminated from the body. Natalizumab was detected in small but increasing amounts in the breast milk of one patient a number of weeks after treatment initiation (37). The drug is probably metabolised in the intestines. Its use may be compatible with breastfeeding, but there are insufficient data to conclude this for certain (36).

Treatment of relapse

Relapses are rare during pregnancy, but occur frequently postpartum. Methylprednisolone shows little transfer across the placenta, and a standard course of treatment lasting three or five days is probably safe also in pregnancy (9). However, a moderately increased risk of cleft lip and palate has been reported following prolonged use of corticosteroids in the first trimester, and particular caution is required early in pregnancy (6). There is little indication that the routinely administered dose of 1 g is more effective than lower doses.

Methylprednisolone passes into breast milk, and breastfeeding should be postponed for the duration of treatment. Immunoglobulins are considered safe during both pregnancy and breastfeeding, and have been used for the treatment of relapses (8). However, their effectiveness is less certain, and in our opinion severe relapses should be treated with methylprednisolone instead.

Conclusion

Women with multiple sclerosis can become pregnant and give birth, and in many cases can also breastfeed. Considerations regarding pregnancy and family planning should be an integral part of decisions over the course of treatment.

The risk of teratogenicity should be con-

sidered carefully when choosing immunomodulatory therapies for women of childbearing age. Strict application of the precautionary principle, with discontinuation of all immunomodulatory therapy before conception is attempted, exposes women with aggressive disease to considerable health risks. These must be weighed against the potential risk to the fetus.

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