Pregnancy in Multiple Sclerosis

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Key Words

Breastfeeding · Disease-modifying treatments · Multiple sclerosis · Pregnancy · Relapse

Abstract

Background: The incidence of multiple sclerosis (MS) is increasing, particularly in young women (20–40 years). In line, experience in the management of pregnancies and use of disease-modifying therapy (DMT) in women with MS is accumulating. **Summary:** Fertility is generally not affected in MS. If assisted reproduction techniques (ART) are required, unsuccessful procedures are associated with an increased relapse risk, particularly in the first few months post-ART. During pregnancy, the risk of relapse declines continuously, especially in the third trimester, then increases early postpartum (3 months) and returns to pre-pregnancy levels at 4–6 months. The progression of MS disability is probably not influenced by pregnancy. Obstetrical outcomes show no increased risk for miscarriage/malformations, and the course of pregnancy is similar to that of women without MS, but with a tendency towards assisted delivery/cesarean section and reduced birth weights. Safety data regarding DMT in pregnancy and breastfeeding are limited. Exclusive breastfeeding may be beneficial and, hence, should not be discouraged in favour of resuming DMT except in cases of highly-active disease. **Key Messages:** The course of pregnancy in women with MS is broadly similar to that in women without MS; risk-to-benefit assessments are warranted when considering halting DMT before pregnancy and resuming DMT postpartum.

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Oral Contraceptives and Risk of MS

Oral contraceptives (OC) are commonly used worldwide. The results of a well-matched case-control study ($n = 305$) adjusted for MS risk factors (age, live births, abortion, body mass index, smoking) showed an increased risk of MS with use of combined OCs: odds ratio [OR] 1.44 (95% CI: 1.14–1.82). The hormonal influence of contraceptive use may explain, in part, the increasing prevalence of MS predominantly in women [1].

German MS and Pregnancy Registry

In 2006, and in alliance with the German MS patient organization, physicians, neurologists and nurses, a nationwide MS pregnancy registry was formed in Germany to assess the course of pregnancy in MS, effect of disease-modifying therapy (DMT), pregnancy outcomes, breastfeeding, and hormones used during assisted reproduction techniques (ART). Data are collected prospectively by standardized interviews every 3 months during pregnancy and up to 24 months postpartum.

Fertility and Infertility in MS

MS often occurs in women aged 20–40 years and pregnancies are not uncommon in MS clinical trials indicating that, in general, fertility is not reduced. However, women with MS tend to have fewer children, even before diagnosis, and undergo ART more frequently, possibly

due to a higher incidence of hormonal disorders such as hyperprolactinemia, decreased estrogen levels, thyroid disorders and endometriosis [2]. With regard to DMT, short-term methylprednisolone pulse therapy does not appear to have an adverse effect on fertility, whereas menstrual disturbances have been reported with interferon-beta (IFN- β) and permanent amenorrhea with mitoxantrone, especially in women older than 35 years [2].

Assisted Reproduction Techniques

ART in MS is associated with a significantly increased relapse risk, particularly in the first 3 months after unsuccessful cycles [3, 4]. The risk appears to be greater with use of gonadotropin-releasing hormone (GnRH) agonists (versus antagonists) for hormonal downregulation, but this observation requires further confirmation. Possible mechanisms for relapse include GnRH-related factors (e.g. inducing the proliferation of immune cells, increase in the production of cytokines/chemokines and endothelial growth factor), fluctuations in estrogen levels (e.g. increase in β -cell mediated factors), dose-effects, immune cell transmigration across the blood-brain barrier, rapidly-changing hormone levels, stress, and absence of MS therapy. ART is possible in women with MS but the disease should be stabilized before patients undergo the procedure.

MS and Pregnancy in General

The typical course of MS during pregnancy was investigated in a prospective European study [5]. Among 269 pregnancies, the frequency of relapses declined up to the third trimester (80% reduction), increased in the immediate postpartum period and returned to pre-pregnancy levels at 4–6 months (fig. 1). Although a higher relapse frequency before pregnancy and relapses during pregnancy were associated with an increased risk of postpartum relapses, most of the increased risk could not be explained.

Relapses during pregnancy can be treated with corticosteroids but caution is advised prior to gestational week 12 because of the risk of cleft palate. In the case of severe relapse in the first trimester, the preferred treatment is prednisolone as it is inactivated in the placenta; only about 10% reaches the fetus versus 100% with dexamethasone. In women receiving continuous corticosteroid therapy, rare cases of premature rupture of the mem-

Fig. 1. Natural history of multiple sclerosis (MS) relapses during pregnancy. Reproduced from [5] with permission.

branes, electrolyte disturbances, and hypoglycaemia have been reported.

Importantly, pregnancy appears to have no influence on the progression of disability in MS. With regard to obstetrical outcomes, the course of pregnancy is similar to that of women without MS but with a tendency towards assisted delivery/cesarean section and possibly lower neonatal birth weights. MS confers no increased risk for miscarriage or congenital malformation.

Pregnancy and Disease-Modifying Treatments

Despite the approval of DMTs in MS >20 years ago, data regarding their use in pregnancy is limited (table 1). Animal studies have tended to use high doses, which may influence outcomes not reflected in clinical trials in humans. Of the various options, glatiramer acetate (GA) has the most favorable US Food and Drug Administration (FDA) pregnancy label (Category B); however, a systematic review concluded that further research was necessary as studies were small [6]. Based on available data, IFN- β and GA appear to be most suitable for use up until the time of confirmed pregnancy. In very rare cases of relapse during pregnancy, their use may be continued if potential benefits outweigh the risks.

Natalizumab is a large molecule that is unlikely to cross the placental barrier to any great extent during early pregnancy. Current recommendations are that natalizumab be discontinued at a maximum of 3 months prior to pregnancy. After consideration of the individual risk-benefit, natalizumab may be given until pregnancy is confirmed or, in rare cases, the benefit of continuing natalizumab during

Table 1. Disease-modifying therapy (DMT) and pregnancy in multiple sclerosis

DMT	Animal studies	FDA pregnancy risk category	Pregnancies during exposure, n	Obstetrical outcomes/risks	Caveats for DMT exposure
Interferon- β	increased risk of miscarriage	C	>1,000	no increased risk of miscarriage/malformations; lower mean birth weight/length; increased risk of preterm birth; evidence from studies suggests potential harm	no need for elective pregnancy termination
Glatiramer acetate		B	>300	no increased risk of malformations, abortions, preterm births or reduced birth weight	further research required as studies to date have been small
Natalizumab	not teratogenic; increased risk of miscarriage	C		no increased risk of malformations; 40% of natalizumab-treated patients have relapses during pregnancy; natalizumab crosses into breast milk	if administered during last quarter of pregnancy, haematological screening of the neonate is required
Fingolimod	teratogenic	C	280	65 healthy newborns; 27 spontaneous and 49 induced abortions; 6 malformations (no pattern)	long half-life ($\approx$ 9 days); adequate contraception advised for 2 months after treatment cessation; breastfeeding is contraindicated
Teriflunomide	teratogenic	X	70	29 induced and 8 spontaneous abortions; 26 healthy neonates; 7 ongoing pregnancies; no pattern of malformations in $\approx$ 100 leflunomide-exposed pregnancies	planned conception not recommended; if pregnancy occurs, a teriflunomide elimination procedure with cholestyramine or activated charcoal is recommended
Alemtuzumab		C	72	32 healthy neonates; 16 miscarriages; 9 abortions; 1 stillbirth; 11 outcomes unknown	thyroid autoimmunity interaction with fertility; allow 4 months after last cycle before pregnancy
Dimethyl fumarate	not teratogenic; some embryo and fetotoxicity	C	38	22 healthy neonates; 3 (12%) spontaneous abortions; 7 (28%) elective terminations	

B = Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.

C = Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

X = Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

the entire pregnancy may outweigh the risk of recurring severe disease activity. Active transport of antibodies (including monoclonal antibodies) to the fetus commences near the end of the second trimester and increases up to delivery. If natalizumab is administered in the last quarter of pregnancy, concentrations may be higher in infants than in mothers which can result in (reversible) haematological abnormalities such as thrombocytopenia and anaemia. As such, only experienced MS centers should treat pregnant women with natalizumab during pregnancy and only after careful risk-benefit consideration. It is recommended that a paediatrician be in attendance during delivery and that blood cell count, liver enzymes, haptoglobin and bilirubin be controlled in the newborn [7].

Adequate contraception is advised for at least 2 months after cessation of fingolimod treatment and breastfeeding is contraindicated. Teriflunomide has an FDA pregnancy label of Category X as a result of teratogenicity in animal studies. In the event of exposure during pregnancy, a teriflunomide elimination procedure with cholestyramine or activated charcoal is advised. Pregnancies reported in women taking alemtuzumab occurred predominantly after the second cycle, with no signal for harm with respect to obstetrical outcomes. As alemtuzumab has a half-life of 9–14 days, 3–4 months is required for clearance. No adverse outcomes were associated with gestational exposure to dimethyl fumarate during the first trimester but the number of pregnancies

was few; its half-life of 90 min facilitates a planned pregnancy.

Most treatments for MS symptoms (fatigue, spasticity, depression, pain, bladder dysfunction) have an FDA risk label of Category C. If use is considered during pregnancy, most options justify an individual risk-benefit evaluation and conference with a teratological information service.

Post-Partum Relapse Prevention and the Role of Breastfeeding

A 2012 meta-analysis of 13 studies investigating the association between breastfeeding and MS relapse showed a tendency for fewer relapses in women who breastfed, suggesting that exclusive breastfeeding may reduce early postpartum relapses [8]. Indeed, breastfeeding should not be discouraged in favor of resuming MS medications. If DMT is deemed necessary, IFN- β concentrations in breast milk are a fraction (0.006%) of the maternal dose and GA is unlikely to appear in breast milk, although it cannot be measured directly due to rapid degradation. Immunoglobulin G antibodies (e.g. natalizumab) trans-

fer into breast milk at much lower concentrations than in serum and are largely degraded by the gut; infant serum levels are therefore low. Oral small molecules (e.g. fingolimod, dimethyl fumarate) are generally found at a lower fraction in breast milk than in sera, but are more likely to directly affect an infant's immune/neurological systems due to minimal gastric degradation and slower hepatic clearance. Thus, breastfeeding appears to be safe while a patient is receiving IFN- β and GA, natalizumab and other non-depleting monoclonal antibodies, but not small molecules such as fingolimod and dimethyl fumarate. In women with highly active disease (i.e. controlled pre-pregnancy by natalizumab, fingolimod, or cyclophosphamide) foregoing nursing and resuming DMT as soon as possible after delivery may be necessary.

Disclosures/Conflict of Interest

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