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Multiple Sclerosis and Pregnancy

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Abstract

The high prevalence of multiple sclerosis (MS) in women of fertile age poses an extra challenge in the management of this chronic neurological disease (Ghezzi and Zaffaroni 2008). The recently studied increasing incidence of MS in Europe (Koutsouraki et al. 2010), with a higher female:male ratio (Bentzen et al. 2010) reinforce the importance of updated knowledge in the subject of pregnancy in women with MS. For several decades, these women were discouraged from having children, until knowledge accumulated following the work by Confavreux et al (1998) showed otherwise. In fact, the gestational period has a beneficial role on the MS relapse rate without affecting the long-term progress of the disease (Bennet 2005). It has even been proposed that pregnancy might have a favourable effect of MS in the long term (D'hooghe et al. 2009). This chapter summarises the data in the literature on MS and pregnancy, discussing the effects of one condition on the other, and the reproductive risks for both mother and child. It is important to highlight that some symptoms of MS may determine different approaches to particular problems. For example, spasticity of lower limbs may affect normal delivery and require caesarean intervention, and urinary incontinence may lead to higher use of antibiotics due to frequent bladder infections.

Hormones in Pregnancy and MS

The hormonal changes that occur during pregnancy induce a physiological shift from Th1 to Th2 immune response, reflecting a favourable profile of anti-inflammatory cytokines (Devonshire et al. 2003). This shift may, at least in part, be the reason for the reduced relapse rate observed during pregnancy (Confavreux et al. 1998).

Oestrogen induces the expression of indoleamine 2,3-dioxygenase (IDO) in monocyte-derived dendritic cells (DCs), thereby limiting T-cell proliferation and cytokine production (Zhu et al. 2007; Kahler et al. 2009). The foetal-placental unit produces oestriol, a type of oestrogen that is probably responsible for part of the relative immunosuppressive state of pregnancy. Ultimately, the oestrogenic profile of pregnancy may be favourable to a period of fewer relapses and less inflammation.

Alpha-fetoprotein, an oncofoetal glycoprotein, is another substance typical of pregnancy. The suppressive effect of alpha-fetoprotein on T cells was described over three decades ago (Murgita et al. 1978; Stahn 1978), without changes in the total number of these cells (Birk et al. 1990). Animal studies have shown that T cells from alpha-fetoprotein treated mice had significantly reduced activity towards the encephalitogenic peptide of myelin oligodendrocyte glycoprotein (MOG) (Irony-Tur-Sinai et al. 2006). The same study showed that alpha-fetoprotein also inhibited MOG-specific antibody production, as well as the expression of CD11b, MHC class II and the chemokine receptor CCR5. Recombinant human alpha-foetoprotein is now being considered as a possible treatment for autoimmune diseases, due to its induced changes

in the cytokine profile (McCain et al. 2007). Initial trials on the clinical use of alpha-fetoprotein for MS treatment have provided encouraging results. They showed that alpha-fetoprotein was well tolerated and capable of decreasing various aspects of neuroinflammation, including disease severity, axonal loss, T-cell reactivity and antigen presentation (Nizri et al. 2007).

In summary, all the maternal changes induced by pregnancy have a positive effect on MS inflammation. These beneficial changes are clinically reflected by the reduced relapse rate during the gestational period. No research has ever contradicted this notion.

Reproductive Counselling

Life expectancy is not particularly affected by MS (Ragonese et al. 2008). Therefore, women suffering from MS should not be worried about having a shorter life, with lesser enjoyment of motherhood. However, the uncertainty regarding whether the woman would be able to care for a child, due to progressive physical and cognitive disability is an important issue to be addressed. The more aggressive the disease is, the higher the risk of not being able to provide adequate maternal care. More aggressive MS is usually treated with medications of higher foetal risk, and adequate disease control must be achieved before pregnancy can be considered by the patients. Although pregnancy planning follows strict rules, it is not rare that patients become pregnant at less than ideal conditions.

Counselling on Genetic Issues

Women with MS considering motherhood may be concerned about the genetic risks of MS in their offspring. MS has a polygenic transmission profile, and the absolute risk of the disease in the family is 2% to 4% (Dyment et al. 2004). The evidence for increased MS risk among a patient's relatives should not be a deterrent for childbearing. Epidemiological studies and genomic screening suggest that MS is genetically influenced, although this influence is relatively small and still controversial in several aspects (Oksenberg and Barcellos 2000; Schmidt et al. 2007).

Fertility, Conception and Drugs in MS

Although no reports on specific physiological effects of MS on fertility and conception are available, several particular aspects must be considered. The high rates of sexual dysfunction reported by these patients (Fletcher et al. 2009) may be associated with a variety of neurological symptoms and disabilities, affecting the overall quality of sexual life (Tepavcevic et al. 2008). Weakness, spasticity, lack of coordination, spasms, depression, bladder and bowel dysfunction, sleep disorders, pain, paroxysmal disorders and sensorial abnormalities may severely affect the sexual life of patients (Demirkiran et al. 2006).

In addition to the above mentioned aspects of MS, many drugs used to treat the disease and its related symptoms are not safe for use during pregnancy. The Food and Drug Administration (FDA) classification specifies that there are no safe (Class A drugs) for pregnant women with MS. Class B includes drugs with no evidence of harm to the fetus, although this conclusion was achieved without a proper controlled trial. Glatiramer acetate and immunoglobulin are the two immunomodulatory drugs in this category. Class C includes drugs that deserve special consideration regarding risk-benefit, since animal studies have shown a degree of harm to the fetus. Beta interferon

and corticosteroids are the typical drugs often used in MS that belong to this category. Class D drugs have evidence of fetal risk, and should only be considered in life-threatening situations or when safer drugs have proven to be inefficient. Azathioprine, cyclophosphamide and mitoxantrone are examples of Class D drugs. Finally, drugs with extremely high risk, positively associated with birth defects, are considered to be class X and should not be used for potentially fertile women. The typical example of a drug in this category is methotrexate.

Other drugs, beyond immunomodulatory or immunosuppressive agents, may often be used by women with MS. Oxybutynin used for incontinence and pemoline used for fatigue are Class B drugs according to the FDA classification. Several commonly used drugs for MS symptoms are classified as Class C drugs: baclofen and dantrolene for spasticity, gabapentin and carbamazepine for paroxysmal disorders and pain, amantadine and potassium channel blockers for fatigue, as well as the selective serotonin reuptake inhibitors frequently used for depression. Benzodiazepines and phenytoin used for pain and sleep disorders are Class D drugs. In summary, a non-planned pregnancy in a patient without proper disease control brings the inherent risks of the drugs in use, even if MS itself does not pose a serious threat to the mother and child.

In 1995, Runmarker and Andersen had already reported the beneficial effect of pregnancy in MS, parallel to lower fertility in MS women. Those results may have been a reflection of a reduced propensity to conception and maternity, particularly in cases with no proper counseling and disease control.

MS Treatment During Pregnancy

Immunomodulatory and immunosuppressive drugs used for MS treatment aim to reduce the frequency and severity of relapses, as well as to delay disability. Ideally, women intending to become pregnant should interrupt their treatment for at least three months prior to conception. The safety of MS drugs used during pregnancy can only be obtained from reports of pregnancies that occurred during the use of these drugs. Therefore, no firm conclusions can be drawn with regard to the safety of these drugs and the general recommendation continues to be the withdrawal of all treatments prior to conception (Ferrero et al. 2006).

Over the last few years, specific studies on the subject of drug exposure during pregnancy in MS have reported on populations from Sweden (Sandberg-Wollheim et al. 2005), Canada (Boskovic et al. 2005), Spain (De las Heras et al. 2007), Finland (Saraste et al. 2007), Italy (Patti et al. 2008), Germany (Hellwig et al. 2008), Argentina (Fernandez-Liquori et al. 2009) and Brazil (Fragoso et al. 2009). The Swedish study concluded that pregnancies in which there was no exposure to the interferon beta 1a *in utero* for at least a two-week period prior to conception resulted in healthier infants than did pregnancies with such exposure. Despite the small population in this study and the lack of statistically significant findings, this report concluded that it was advisable to stop using interferon beta 1a before conception (Sandberg-Wollheim et al. 2005). The Canadian study confirmed this conclusion, reporting on a small number of pregnancies exposed to interferon beta, with significantly higher risks of abortion, low birth weight and prematurity (Boskovic et al. 2005). The Spanish study included a larger number of patients and did not find a significantly higher rate of complications for those accidentally exposed to immunomodulators (De las Heras et al. 2007). The Finnish

group did not concentrate on drug exposure and its possible complications (Saraste et al. 2007), while the Italian group concluded that there was no indication for terminating pregnancy in MS women exposed to interferon beta in the early stages of pregnancy (Patti et al. 2008). The German study reported on higher incidence of low birth weight among mothers with MS, even without the use of immunomodulators (Hellwig et al. 2008). Meanwhile, in South America, the Argentinean group reported a much higher rate of complications (Fernandez-Liquori et al. 2009) than did the Brazilian group (Fragoso et al. 2009). In general, even the higher incidence of complications reported by some groups was only slightly higher than that of a general population, except for abortions. However, abortions reported in all studies included miscarriages and termination of pregnancy, the latter many times due to worries on drug exposure. Few data on pregnancy complications from the recently licensed natalizumab are available, but a post-marketing surveillance program showed that all induced abortions performed because of fears of birth malformations presented normal fetuses. No teratogenic effect of natalizumab has been reported on animals (Wehner et al. 2009).

The lack of definitive data on the subject of drug exposure in pregnant women with MS leads to the general recommendation that women who intend to become pregnant should not be using medications of any kind. At the same time, women who could potentially become pregnant should preferentially receive Class B medications for MS and its symptoms, since there are no Class A drugs for these conditions according to the FDA.

MS and Delivery

In general, the delivery method is decided taking into consideration the obstetric indications rather than the presence of MS. Overall, the rate of caesarean operations had been reported to be similar to that of women without MS (Mueller et al. 2002). However, in 2009, Kelly et al reported on a very large database in the United States, showing that, indeed, the rate of cesarean section in MS is considerably higher than in non-MS.

Special attention should be given to preoperative evaluation, in order to decrease neurologically related postoperative complications in these patients. Early deambulation and avoidance of bladder-related disorders are particularly important in these cases. Regarding the type of anesthesia, epidural injection seems to be safer than spinal block (Dorotta and Schubert, 2002), since the latter has been previously reported to possibly be associated with neurotoxic effects (Vercauteren and Heytens, 2007). Patients should be informed about the anesthesia plan and need to be aware of possible complications.

Although very rare, and basically related to spinal cord lesions, autonomic dysreflexia can occur in women with MS (Bateman and Goldish, 2002). In this condition, hypertension and compensatory parasympathetic overactivity may lead to complications that require vigorous intervention (Argyriou and Makris, 2008).

Data from the large Norwegian Medical Birth Registry have shown that, independently of MS treatment and disease stage, the neonates presented lower birth weight and height, and more interventional delivery was reported (Dahl et al. 2005; 2006; 2008). Similar results were reported from a Taiwanese database (Chen et al. 2009).

Relapse Risk After Delivery

The increased relapse risk after delivery, in comparison to the gestational period, is not contested by any author. In fact, the abovementioned beneficial effects from pregnancy on the course of MS explain the changes in relapse rate reported by all authors. Once this beneficial profile changes after delivery, the relapse risk increases. Additionally, the rapid increase in interferon gamma-producing T cells may be a contributor to this relapse rate increment (Langer-Gould et al. 2010). The risk of relapse during the postpartum period is greater for women with higher relapse rates and higher EDSS before pregnancy (Vukusic et al. 2004). The slightly longer hospitalization period for MS mothers does not seem to relate to higher rates of complications but rather, to a more prudent attitude among obstetricians (Ferrero et al. 2006).

Although not deeply studied, there are data from few studies discussing the rationale for using corticosteroids or immunoglobulin during the immediate postpartum period. This approach would be important to avoid relapses in this period, and the results from these few studies seem promising (De Seze et al. 2004; Achiron et al. 2004; Ringel and Zettl, 2006; Hellwig et al. 2009).

Breastfeeding

The rate of breastfeeding among women with MS varies widely in the literature. Cultural issues, personal considerations and family advice seem to be important for the patient, and the doctors do not appear to have a definite position regarding the matter. Therefore, recommendations on breastfeeding seem to be taken individually, without evidence-based studies. The higher risk of relapses during the postpartum period may lead physicians to discourage breastfeeding, so that immunomodulatory or immunosuppressive treatment can start early after delivery. An American survey showed that only 11% of all physicians allowed medications during the breastfeeding period, and that the medication allowed was mostly glatiramer acetate (Coyle et al. 2004). The same survey showed that neurologists preferred to leave the decision on breastfeeding to the patient.

The transfer of large molecules such as interferon beta to the human milk is unlikely to be significant. There are no studies regarding the levels of immunomodulatory and immunosuppressive MS drugs in human milk or, indeed, regarding whether the oral intake of these amounts by the child might be significant. As a general rule, breastfeeding can be allowed for women using FDA Class A or B drugs, although for Class B, breastfeeding could be intercalated with bottled milk formulas, thereby reducing the risk of excessive exposure.

Recent data on a possible protective effect of breastfeeding in the post delivery relapse rate may be another point towards encouraging breastfeeding (Langer-Gould et al. 2009).

Long-Term Effects of Pregnancy on MS

The long-term relapse rate, disability and disease evolution do not seem to be affected by pregnancy in women with MS. There are no reports suggesting otherwise, and major

reviews have emphasized that, over the long term, pregnancy does not alter the course of MS (Houtchens, 2007; Lee and O'Brien, 2008; D'hooghe et al. 2010).

Conclusion

The reasons for anxiety in women with MS who consider pregnancy are not difficult to comprehend. These patients need to be reassured that pregnancy, in itself, does not seem to affect the disease negatively and that MS does not affect pregnancy outcomes negatively. Understandably, women with MS are concerned with their own health and well-being, the well-being of the child, the difficulties in experiencing and coping with motherhood, social attitudes and the pressure on decision making (Houtchens, 2007). A considerable lack of knowledge in female MS-patients concerning the interactions of MS and pregnancy has been recently reported (Albretch et al. 2010). Unfortunately, many physicians are equally unsure about the subject and cannot help the patient's decisions. Lack of knowledge has led to several cases of induced abortions of normal fetuses and still creates a high degree of anxiety and insecurity among women with MS and their relatives, as well as among obstetricians and neurologists caring for these patients. Additional care may be necessary in women with higher degrees of neurological disabilities and fatigue, in order to facilitate the adaptation to motherhood (Smeltzer 2007).

Conflict of Interest

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