Mini Review

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Pregnancy in Multiple Sclerosis

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Summary

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) that affects 2.3 million people worldwide, mostly young adults, with a high female prevalence (70% to 75%). Therefore, most individuals who get diagnosed with MS are women of childbearing age. However, disease activity is greatly reduced during the last trimester of pregnancy, although an increased relapse rate is observed in the three months after delivery. Despite several studies point to pregnancy as a period of stabilization in the clinical course of MS, pregnancy in MS remains a controversial issue, mainly in relation to discontinuation of disease-modifying treatment, which is recommended from the time pregnancy is established and, to date, remains confirmed. Therefore, this is a very sensitive issue to consider given the importance of, on the one hand, ensuring the health of the fetus and, on the other hand, the health of the woman about both the accumulation and progression of the disease.

1. Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system (CNS), affecting 2.3 million people worldwide, with a prevalence ratio of women to men markedly increase during the last decades (2.3–3.5:1) [1-6]. In addition, MS is the most common cause of non-traumatic neurological disability in young adults that typically presents during the ages of 20–40 years [7,8]. Therefore, most individuals obtaining the diagnosis of MS are women of child-bearing age [3]. Several retrospective studies have shown a significant an approximately 80% reduction of relapse rate during pregnancy especially in the third trimester, while other studies have reached different conclusions showing that pregnancy does not substantially modify the course of the disease [9-14]. Beneficial effects of pregnancy may in part be due to the immunomodulatory properties of steroid hormone [15]. This can be explained by the fact that, during pregnancy, the production of hormones, including estrogen, progesterone, prolactin, and glucocorticoids, results in a state of immunotolerance, leading to a decrease in inflammation, which, in contrast, is a typical feature of MS relapses. Indeed, in MS pathogenesis, CNS infiltration by autoreactive lymphocytes and T cell-mediated responses directed against antigens in the myelin sheath likely play a central role in its development [16]. Nevertheless, and most importantly, several works have demonstrated a higher risk of relapse in the three months post-partum as compared with the rate during the year before pregnancy, especially in women with higher disease activity and a high level of physical disability in the year before pregnancy [17-20]. In this scenario, it is therefore important that pregnancy in MS be proactively discussed, especially when considering disease-modifying treatments (DMTs). Early treatment with DMTs reduce/delay long-term disability [21]. These drugs do not appear to cause any major fetal malformations, however current recommendations are to withdraw DMTs prior to conception, leaving patients exposed to an uncertain period of untreated disease because it is not yet clear how they may affect the immune system of the developing fetus [22]. Indeed, limited evidence of DMTs safety in pregnancy limits or delays their use with consequent risk of aggravating the course of the disease in women with MS who wish to become pregnant or have an ongoing pregnancy. At the same time, however, discontinuation of therapy has been associated with a return of disease activity and rebound [23]. Thus, the medical management of MS during pregnancy and the postpartum period is challenging given the risks of medication exposure to the fetus in utero and to the infant through breast milk [24]. This mini review focuses on the biological and clinical effects of pregnancy in MS patients, particularly the available evidence regarding the impact of pregnancy on disease activity and therapeutic management during pregnancy and in the postpartum period.

2. Increasing Ratio of Women to Men in Relapsing-Remitting MS.

MS is the most common acquired inflammatory demyelinating

disorder of the CNS, manifesting an extremely variable clinical course, which were summarized in three phenotypes: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS) [25]. For RRMS patients, clinical onset is characterized by inflammatory attacks (relapses), causing neurological symptoms, followed by remitting deficits, that often will convert to SPMS form, characterized by a gradual worsening of neurologic function in the absence of remissions while an unremitting increase of disability is found since the onset in PPMS subject [26,27]. According to the newly categorization, the different clinical courses can be summarised in relapsing MS (RMS) and progressive MS (PMS) [6,27]. Recently, serial cross-sectional studies have shown progressive increase in MS incidence in adult women in the last 30 years, specifically in RMS patients, but not in PMS patients [28]. Despite no causative factors have been identified to explain this increase, possible underlying causes for the gender disparity in MS have been indicated, such as diet, later childbirth, hormonal replacement therapy, obesity, smoking and vitamin D deficiency [28,29]. Among these, vitamin D deficiency seems to be the principal factor involved in this male-female disparity [30]. Not surprisingly, vitamin D supplementation is now used in clinical practice, since the association between vitamin D and MS pathogenesis, its exact effect in preventing MS, which is a complex disease caused by the interaction of genetic and environmental factors yet to be investigated.

3. Pregnancy Implications for MS Disease Activity and Progression

MS does not affect a woman's ability to conceive and carry a fetus to term, just as the diagnosis of MS does not increase the rate of premature births or deaths, birth defects, cesarean deliveries, or miscarriages [28,31-33]. Nerveless, the impact of pregnancy on the long-term course of the disease and disability in MS is still unclear. In this regard, several studies have suggested that pregnancy has no effect on long-term outcome in MS, whereas others indicated that pregnancy is potentially beneficial [34,36-42]. Benefits include reduced risk of excessive gestational weight gain, gestational diabetes and preeclampsia [43]. However, these studies were limited by relatively small sample sizes and retrospective data collection [6]. The most accepted theory to explain the protective effect of pregnancy on the disease activity in women with MS is that estrogens and other sex hormones, rises continuously during pregnancy and maximizes in the last trimester, activate immunological transformation during pregnancy by shifting T helper cells to mostly Th2 (anti-inflammatory effect) rather than Th 1 (pro-inflammatory effect), while the opposite occurs in the postpartum period [44]. Animal studies on experimental autoimmune encephalomyelitis (EAE) showed reduced demyelinating lesions number administration of estrogen receptor-alpha ligand, demonstrating the anti-inflammatory and neuroprotective impact of estrogens, especially estradiol [45]. In support of the protective effect by estrogen in the animal model, in a multicenter clinical trial non-pregnant women with RRMS who took estrogen-containing oral contraceptive in addition to interferon-β1a treatment had a significant reduction in active lesions compared with those who received interferon-β1a alone [46,47]. On the contrary, the increased risk of relapse in the immediate postpartum period, due to an increase in Th1 cytokines, suggesting that early reinitiation of DMTs may be beneficial, although the early postpartum relapses notably have a poor prognostic value for what concerns MS disability progression [48,49].

4. Disease Modifying Treatment During Pregnancy

The use of DMTs during pregnancy is still debated, as information on their safety in pregnancy is limited as there are no reliable trials and well-controlled studies in humans [28,46]. Therefore, the risk of continuing or discontinuing treatment must be evaluated on a case-by-case basis, considering the priorities, age, severity of disability, and disease activity of the patient [46]. In general, discontinuation of DMT is recommended before and during pregnancy since all DMTs have potential adverse effects on fertility and pregnancy outcomes [50]. However, in patients with high disease activity, whose risk of drug discontinuation would lead to an increased risk of relapse, interferon-β and especially glatiramer acetate can be continued [46]. In addition, a recent study has shown that natalizumab use is also advisable during pregnancy since it correlates with a lower risk of MS relapse [51]. Nevertheless, evidence on the safety of natalizumab continuation is limited.

5. Conclusion

MS is considered to have no effect on fertility, pregnancy or fetal outcomes. Similarly, pregnancy does not seem to aggravate the disease, but rather appears to beneficial in women with MS, being associated with a reduction in relapse especially during the third trimester. Although pregnancy is associated with an increased risk of relapse immediately postpartum, the lack of negative effects on long-term disease course and disability. Regarding the use of DMTs, their use is still limited, although several MS drugs are safely used in pregnancy. Overall, these results represent an important message to MS patients that they should be supported during pregnancy and encouraged to have children.

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