Multiple sclerosis in pregnancy –
current neurological considerations

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ABSTRACT
Multiple sclerosis (MS) is a neurological condition found in young women of reproductive age, and pregnancy can be a challenge. Lack of consensus on the conduct and impact of MS on pregnancy outcomes requires adequate counseling for these patients. Early initiation of treatment in MS to prevent long-term disability is extremely important because delaying treatment after the woman achieves irreversible complications may accompany reproductive goals. Aggression and disease progression requires an ideal schedule for conception. Initiation of treatment and successful pregnancy monitoring are clear goals of healthcare providers. Counseling of patients with MS before pregnancy, conduct during pregnancy, mode of delivery, and postpartum management, to which is added the choice of type of medication are important criteria that prevent complications secondary to the clinical course of this disease.

Keywords: multiple sclerosis, pregnancy, neurological impairment, perinatal results

INTRODUCTION
Multiple sclerosis (MS) is a disease that belongs to the neurological spectrum, characterized by chronic inflammation. Moreover, MS is a degenerative disease mediated by immune mechanisms without having a negative effect on fetal development, registering a postpartum increase in its activity. This condition affects the central nervous system (the brain and the spinal cord), destroying the myelin sheath without the possibility of its subsequent regeneration. MS concerning often affects young people, with a peak between 20 and 40 years, and is more common in women than men [1], which means that we also find this disease in pregnant women [2]. Regarding the Europeans, MS has a prevalence of 83:100.000 and an annual incidence of 4.3:100.000 [3].

The causes of MS are not fully elucidated. It is believed that there is a combination of genetic factors and immunological factors over which the environmental factors act. Among the environmental factors, a major impact is low sun exposure, smoking, Epstein-Barr virus, and low vitamin D levels [4,5].

MS does not fall into genetic diseases, but there is a genetic predisposition in individuals with a family history of the disease. Immunogenetic studies have shown that the susceptibility to MS increases by 20-60% in the case of genetic variations in the human leukocyte antigen (HLA) system, the main alleles incriminated being HLA-DRB1 * 15:01, MHC DR15, and DQ6 [6,7].

The diagnosis is based on the clinical aspects and identification of brain and spinal cord lesions on MRI [8]. Being a more common disease among young adults, a major concern among women with MS is the effect of the disease and treatment on fertility, respectively, pregnancy and fetus. One positive thing is that fertility is not affected, and in addition, the symptoms may even improve during pregnancy. MS treatment is not etiological but aims to restore function and prevent relapses. Corticosteroids are used with the first intention to relieve symptoms. For recurrent-remissive forms, it is necessary to administer disease-modifying treatments (DMT), which can cause fetal injury, therefore it is recommended to discontinue it before conception. [9]. One-third of women receiving pre-pregnancy DMT could relapse in the first trimester [10], making management difficult. Thus, women are advised to become pregnant...
during the period of low disease activity, stabilized by treatment.

This article summarizes information on pregnancy-related issues in women with MS, counseling, and treatment related to pre-pregnancy, pregnancy, and postpartum periods.

**CLINICAL ASPECTS OF MS**

The preclinical phase of the disease, from exposure to the incriminated risk factors until the onset of symptoms, can take 10-20 years [11].

Currently, four clinical courses of MS are used: clinically isolated syndrome (CIS), relapsing-remitting (RRMS), secondary-progressive (SPMS), and primary progressive (PPMS) [12]. CIS is the first episode of neurological symptoms secondary to inflammatory demyelination that lasts at least 24 hours and has similar to MS lesions on brain MRI. These patients are at risk of developing MS, and prompt therapeutic intervention at this time with DMT may delay the onset of MS. The second category, RRMS, is the most common, being the first form of presentation in 85% of patients with MS. It includes cases with episodes of new neurological symptoms - relapses or exacerbations of pre-existing symptoms, with more or less obvious clinical remission between outbreaks of the disease but which does not progress clinically. The third form, SPMS includes patients who do not fully recover from a recurrent episode and continuously evolve the disease gradually, with the aggravation of neurological symptoms and the onset of disability. The final form, PPMS is characterized by severe impairment of neurological function from the onset of symptoms, few moments of symptomatic relief or plateau phases, and without recurrences, exacerbations, or early remissions [8,12,13].

Symptoms vary from person to person depending on the damage to nerve cells in the brain and spinal cord. Thus, patients experience sensory, motor, autonomic, or visual symptoms. Clinical aspects are weakness more or less associated with muscle pain, chronic fatigue, dizziness and vertigo, cramps, tremor, imbalance in gait or in fine movements, to which are added ophthalmic, urinary, and digestive symptoms [11,14,15].

Unfortunately, MS is a disease that cannot be cured; on the contrary, evolution is getting worse. The diagnosis of MS is mainly clinical, supplemented by MRI examination. Thus, the correct inclusion in one of the 4 types of MS is important for prognosis and treatment [12,16].

**FERTILITY AND PREGNANCY**

Endocrinological changes occur in women with an active form of MS, but the progression of the disease and its treatment do not appear to affect major fertility, so young women suffering from this disease have no difficulty getting pregnant. There was also no evidence of an increased risk of miscarriage or ectopic pregnancy in these patients [10,17].

In pregnancy, many hormonal changes lead to an immune-suppressive status, so most of the time, pregnant women have a plateau phase of the disease without exacerbations or periods of aggravation, but clinical activity increases significantly in the first trimester after birth [10]. In contrast, Nguyen et al. showed a delay in the first clinical manifestation of MS by at least 3 years in women with previous pregnancies and births versus those who had never had a pregnancy, exclusive breastfeeding being considered a way to prevent postpartum reactivation [18]. In addition, Ponsonby et al. found that each child born reduces the risk of a first clinical attack of MS by 49% [19]. However, 15-30% of women with MS have recurrences during pregnancy, especially if they have relapses in the year before pregnancy or after cessation of DMT, have a severe disability, or are younger than 35 years [9].

Estrogen and progesterone levels during pregnancy provide some relief from common symptoms. Given that the maximum level of these hormones is reached in the last trimester of pregnancy, then the pregnant woman benefits the most from their neuroprotective, remyelinating, and anti-inflammatory role. In addition, estrogen provides normal neurological development in fetuses from mothers with MS. The hormone HCG (Human Chorionic Gonadotropin) acts on the immune system by reducing its activity and inflammation [10,15,17].

Since MS generally progresses to worsen, it is recommended that women become pregnant as soon as possible before the onset of a clinical form of the disease [20]. It is preferable for a woman to become pregnant spontaneously because assisted reproduction techniques increase 7 times the risk of exacerbation of MS and 9 times the risk of increased disease activity, especially when GnRH analogs are used [17,21].

As a consequence of the pressure of the pregnant uterus on the neurogenic bladder and the intestine, pregnant women with MS have an increased risk of urinary tract infections (27%) compared to the general population (16.4%). There is also an increase in upper respiratory tract infections [22].

There are some particularities regarding pregnant women with MS, namely that there has been an increase in the incidence of fetuses with small for gestational age (SGA) but without perinatal complications [22,23]. Another study found no significant association with infants’ gestational age or birth weight [24]. Also, there is a risk of preterm birth, most likely due to neuronal dysfunction of the pelvic organs [22].
In general, women with MS can give birth vaginally without problems, but pregnant women who have more severe muscle damage are at risk of requiring cesarean section or instrumental delivery. There has also been no evidence of an increase in the rate of birth defects in these women [25,26]. However, in women with MS, no more labor induction, presentation abnormalities, the prolonged second stage of labor, or postpartum hemorrhage have been demonstrated [9].

A comparison between pregnant women’s complications with MS and the general population was suggested by some studies, and there was no increase in the risk of preeclampsia, gestational diabetes, or abnormal placental adhesion [27].

After a prior anesthetic consultation, pregnant women with MS should benefit from neuraxial analgesia during labor, the premise that anesthetics have neurotoxic potential on the demyelinating areas of the spinal cord being dismantled. Given the spasticity present in these cases, the use of epidural anesthesia and/or benzodiazepines during labor is even indicated, not being associated with postpartum recurrence [9,28].

**TREATMENT OF MS DURING PREGNANCY**

Curative treatment for MS does not exist, but some therapeutic options influence the evolution and can be used safely in pregnancy. One of the largest studies conducted by Dr. Vilija Jokubaitis from Monash University includes 9,000 women with MS, of which 1521 became pregnant. Furthermore, 42% of them became pregnant while receiving specific treatment, 20% became pregnant from the first year after stopping the treatment, and 39% of pregnant women had been treated for more than one year before conception. The study results showed no differences between the three mentioned groups regarding pregnancy, childbirth, or the associated complications such as premature birth or abortion. As an exception, only those who had risky treatment during pregnancy had an abortion [29].

Before pregnancy, a period of 1 year without relapse of MS is recommended, with discontinuation of teratogenic DMT (e.g., fingolimod, teriflunomide, siponimod, ozanimod, cladribine, ponesimod, ocrelizumab) 10 days, up to 1 year depending on the substance. It is unnecessary to stop taking beta interferon, glatiramer acetate, dimethyl fumarate, natalizumab. Fingolimod and natalizumab are known to be at risk of severe relapse and should be avoided preconceptionally. According to the general guidelines, pre-conception supplementation with folic acid and vitamin D is recommended [10]. Currently, beta-interferon (IFN-β) and glatiramer acetate (GA) tend to be the most appropriate drugs until pregnancy is confirmed, and therapy can be continued in case of recurrence during pregnancy by analyzing the risks versus the benefits [10].

Since many women no longer have symptoms during pregnancy and the disease does not progress, most do not require treatment. But there are also some cases in which some women become pregnant when they have an active and more advanced form of the disease, and therefore they need special treatment.

The first-line treatment for pregnant women with active disease is beta-interferon and glatiramer acetate if the benefit of administration justifies the potential risk to the fetus. They relieve the symptoms of exacerbations and slow down the disease's progression [1,10,30].

If there are relapses, corticosteroids (methylprednisolone or prednisone) can be used during pregnancy and lactation [28,31]. The recommended dose of methylprednisolone is 1g per day for 3-5 days during the onset, sufficient to relieve symptoms. The administration should be avoided during the first trimester of pregnancy in order not to appear malformations. In addition to these drugs, natalizumab can be used in pregnancy, every 6-8 weeks, up to 30-34 weeks gestational age, the risk of affecting the fetus being very low compared to the effect that lack of treatment would have on the mother [28]. Natalizumab administration in the third trimester is associated with hematological abnormalities in infants [10,32].

Considering the risk factors for MS, all pregnant women should continue supplementation with folic acid and vitamin D (up to 4000 IU per day) during pregnancy. There are also good effects in oral treatment with estriol (8mg per day) and estrogen, combined with glatiramer acetate, which over time has led to improved MRI control images [10,28].

**POSTPARTUM AND BREASTFEEDING**

Because after birth, the body returns to the hormonal and immune status before the pregnancy, the recurrence of the disease occurs in 30% of cases three months after birth and 50% in the first six months.

Despite the fears, there was no evidence of an increased association between breastfeeding and MS recurrence, but it has been shown that exclusive breastfeeding for the first few months can lead to a decrease in postpartum recurrences and delay disease progression for at least six months. After these months, most of the symptoms return, the relapses appear, and the condition can be treated according to the neurologist's instructions. Many specific drugs are allowed in breastfeeding, such as beta-interferon, glatiramer acetate, and corticosteroids. Transfer of immunoglobulin G antibodies (natalizumab) into
breast milk is low, but should be administered with caution, only if the maternal benefit is greater than the potential risk for fetal hematological abnormalities. Other DMTs such as teriflunomide, fingolimod, siponimod, ozanimod, cladribine, ponesimod, and ocrelizumab are contraindicated during breastfeeding because they may induce neurological damage to the infant by decreasing gastric degradation [10,14]. Hellwig K. has shown protection in breastfeeding in patients undergoing IFN-β and natalizumab therapy and an increased risk of fingolimod and dimethyl fumarate. In women with the active disease under therapeutic control, it is recommended to resume medication immediately after birth [33].

Monitoring women with MS during pregnancy and the first year postpartum can be done by MRI without or with agent contrast if the woman is not breastfeeding 24 hours after exposure. The use of gadolinium in pregnancy as a contrast agent has been associated with multiple abnormalities (dermatological, rheumatic, inflammatory) and even fetal death in utero or postpartum [34].

The newborn will be carefully investigated to detect the early existence of any congenital condition given to the treatment used by the mother during pregnancy. For example, reversible hematological abnormalities (thrombocytopenia and anemia) will be sought in fetuses from mothers who have received natalizumab during pregnancy [14].

CONCLUSIONS

Multiple sclerosis is an autoimmune disease that mainly affects young women. They do not have fertility affected, can have safe pregnancies, and can give birth to healthy babies. The effect of pregnancy on the evolution of the disease seems to be favorable, with the improvement of the symptoms and the cessation of the evolution. Pregnancy-modifying treatments during pregnancy (corticosteroids, beta-interferon, glatiramer acetate, and natalizumab) do not pose a significant fetal risk and may be administered to women with active disease. The pregnancy of a woman with MS should be monitored by a multidisciplinary team of at least one obstetrician and a neurologist to identify potential maternal and fetal complications that may occur. Vaginal delivery with epidural anesthesia should be encouraged in cases without pelvic floor damage. Prevention or delay in postpartum relapse is done by exclusive breastfeeding and administration of beta-interferon or glatiramer acetate.

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