Multiple sclerosis and pregnancy
Esclerose múltipla e gravidez

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ABSTRACT

Objective: This review discusses aspects of the intention to become pregnant, pregnancy itself, delivery and the postpartum period in patients with multiple sclerosis. Methods: The search was done in the following databases: MEDLINE, THE COCHRANE LIBRARY, EMBASE, LILACS, SciSEARCH, and in references to the most relevant papers in the past ten years. The following terms were used for the research: multiple sclerosis, pregnancy, breastfeeding, beta interferon, glatiramer acetate. Results: Thirty three specific papers on this theme were found, including the international consensus on the treatment of multiple sclerosis. Themes like prenatal, delivery and postnatal management were analyzed. Conclusion: The articles highlight that treatment with immunomodulators is discouraged, and that corticosteroid pulsed therapy is recommended for eventual attacks. Breast feeding, though not encouraged, is not formally contraindicated.

Keywords: Pregnancy; Multiple sclerosis; Immunologic factors; Immunosuppressive agents

INTRODUCTION

Multiple sclerosis (MS) is a T-cell mediated autoimmune disease resulting in demyelination of some central nervous system regions. It is characterized by recurring episodes of neurological dysfunction that reflect immunological alterations. These attacks alternate with variable periods of clinical remission. Neurological symptoms presented clinically result from inflammatory reactions, a reflection of degenerative aggression to demyelinated regions in various neurological functional systems¹². The prevalence of MS is relatively low, especially in Latin America, compared to Northern hemisphere countries.³ Since MS typically affects young women, pregnancy is always of special interest in MS.

An updated review in Portuguese is, therefore, relevant for the management of these cases.

METHODS

The search strategy for papers on this theme followed the recommendations of the Cochrane Foundation, and was done in the following databases: MEDLINE, THE COCHRANE LIBRARY, EMBASE, LILACS, SciSEARCH, and in references to the most relevant papers in the past ten years. The following terms were used singly or in combination: multiple sclerosis, pregnancy, breastfeeding, beta interferon, glatiramer acetate.

RESULTS

We found 33 specific papers on this theme, including the international consensus on the treatment of MS, which referred to pregnancy and the pre- and postnatal period.

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This paper describes the findings in relevant papers specifically focusing pregnancy and pre- and postnatal management.

T-cell mediated autoimmune diseases, such as rheumatoid arthritis and MS, tend to regress during pregnancy due to immunological changes that take place as a result of childbearing(4). Immunological changes reinforce the passage from cellular to humoral mediation. In 2004, Confavreaux et al. conducted a major multicentric prospective study (PRIMS - Pregnancy in Multiple Sclerosis)(5), and observed the natural history of MS in pregnant women in 12 European countries for up to two-year postpartum follow-up. Strict evaluation criteria were applied to study 227 pregnancies after a diagnosis of MS at least a year before the pregnancy. These authors found that the recurrence rate fell 70% during the third trimester of pregnancy and increased during the first three months postpartum compared to one year before pregnancy. They also noted that 72% of patients had no recurrence in the first three months after delivery. The assessment that included the one-year period prior to conception, pregnancy itself, and a one-year period following delivery, revealed that pregnancy did not alter the global rate of disease progression. Another finding was that breastfeeding mothers had fewer attacks of the disease, a situation not explained plausibly, notwithstanding the contrary opinion of Nelson et al.(6)

A few careful studies have shown that MS does not negatively affect fecundity, abortion, prematurity, or preeclampsia rates(5,7), among others. Worthington et al.(9), found that the rates of cesarean section, low-birth weight, child mortality, or congenital anomalies are not different from those of the population at large. Although Dahl et al.(9), described an increased prevalence of induced labor, use of forceps and low-birth weight and short-height, these same authors did not find an increased incidence of congenital anomalies or neonatal mortality. In 2002, Ferrero et al.(10), described an increased incidence of anemia and urinary tract infection in pregnant MS patients.

**PRENATAL, DELIVERY AND POSTNATAL MANAGEMENT**

Prenatal

Treatment of attacks (intermittent use):
The FDA does not formally contraindicate corticosteroids for the treatment of MS attacks during pregnancy. Reports of cleft palate and hypoadrenalism, however, led to the recommendation that the benefit of using corticosteroids should be assessed relative to the risks(11-12). Use of endovenous immunoglobulin during attacks is not related to fetal malformation or complications of pregnancy(13). Both approaches are acceptable for women that may become pregnant during treatment, or during pregnancy and in the puerperium.

Regular and continuous immunomodulatory and immunosuppressive treatment:
According to national and international consensuses, recommendations and guidelines(14-24), women at childbearing age that intend to become pregnant or that do not use effective contraception should not receive continuous treatment with beta interferon. This drug has been associated with fetal loss and low birth weight in patients that became pregnant during treatment(25-26). Discontinuing treatment is, therefore, recommended before conception(27).

Glatiramer acetate is a synthetic polymer used subcutaneously every day. It induces T helper 2 (Th2)-like cells that regulate suppression and interfere with inflammatory T-cell activation(28,30). Glatiramer acetate is safe in that it does not cause congenital defects in animals. Few studies, however, have been done in human beings. Coyle(31) studied pregnant patients exposed to this drug and found normal newborns in 96.3% of cases.

Methotrexate and cyclophosphamide are mutagenic, teratogenic, and strictly contraindicated during pregnancy.

Azathioprine crosses the placenta, but the fetal liver blocks the enzyme that converts this drug into its active metabolite(32). There are no reports of teratogenic effect in humans, but there are cases of prematurity, intrauterine growth restriction, and low-birth weight.

Mitoxantrone is an anticancer drug and a powerful suppressor of the immune system. There are no well-controlled studies on its use during pregnancy, but the beneficial effects are considerably lower than the risks.

In summary, except for glatiramer acetate, which possibly has no harmful effects, all other drugs used for the immunomodulation and immunosuppression of MS are contraindicated for women at childbearing age that wish to become pregnant or that are not using effective contraception.

**Route of delivery.**

Delivery does not offer specific difficulties for MS patients, and the route of delivery is chosen strictly according to obstetrical indications. A recent paper by Dahl et al.(9), on Norwegian patients found a higher rate of induced labor and use of forceps, with a trend that suggests a slower progression rate of the second phase of labor.

**Anesthesia.**

The effects of local and regional anesthetics on the progression of the disease remain unclear. In 1959, Schapira(33) reported that epidural anesthesia should offer lower risks compared to spinal anesthesia, since the concentration of anesthetics in the cerebrospinal fluid is higher in the latter, and demyelinated areas would be more exposed to anesthetics. In 1988, Bader et al.(34), reported
that spinal anesthesia was implied in disease recurrence. This author investigated 32 pregnancies in MS patients and found that women undergoing epidural anesthesia did not have a significantly higher risk or disease recurrence compared to women in which local infiltration or pudendal block was used. Another observation was a tendency for disease recurrence in women that received a high dose of local anesthesia. The author concluded that epidural anesthesia was the best option for MS patients in labor.

**Puerperium**

Treatment of MS is important during this period even if the patient is breastfeeding. The justification is that the incidence of postpartum recurrence of MS is increased, which results in the mother being less able to care for their newborn. Literature is consistent in showing that the postpartum use of endovenous immunoglobulin and corticosteroids reduce the recurrence rate (36,37).

**Breastfeeding**

Breastfeeding as a rule should be encouraged without forgetting that there may be eventual side effects caused by drugs that pass into breast milk. Corticosteroids may affect growth and interfere with endogenous production corticosteroids in the infant. Its use, however, is not formally contraindicated while breastfeeding. There is no restriction on the use of endovenous immunoglobulin. Cyclosporine, mitoxantrone, azathioprine, and methotrexate pass into breast milk, so that breastfeeding is contraindicated if these drugs are used. Harmful effects have not been described as a result of using beta interferon and glatiramer acetate; these drugs appear to be degraded in the infant's stomach. Care should be taken, however, when using these drugs, as few studies have assessed their effects on infants, none of them long-term studies. Since these drugs potentially are highly immunogenic, there is the possibility that degradation products may alter the immunological response of those who used in the neonatal period. As a general rule, these drugs may be used when beneficial effects for the mothers are greater than the possible risks for the infant.

**Future pregnancies**

The natural history of the disease should encourage patients to have their children as soon as possible, except when the disease is active, in which case adequate treatment should be given until remission of symptoms is attained (36-37).

**DISCUSSION**

The papers we reviewed led us to the following guidelines:

1. Treatment with immunomodulatory drugs (beta interferon or glatiramer acetate) in patients that specifically wish to become pregnant should be discouraged; in these cases, treatment should consist of pulsed therapy for eventual attacks of the disease.

2. Glatiramer acetate may be given to women at childbearing age that are using low efficacy contraceptives. Beta interferon may be given to women that do not tolerate glatiramer acetate on condition that they use high efficacy contraception. On learning of a pregnancy, patients using immunomodulators should be guided to discontinue these drugs and corticosteroid pulsed therapy should be used, if needed.

3. During labor, the route of delivery strictly obeys obstetrical indications; anesthetists should be asked to use epidural anesthesia.

4. Patients using glatiramer acetate may continue using this medication postpartum. Although not encouraged in these patients, breastfeeding is not formally contraindicated. Postpartum patients not using immunomodulators should be oriented to breastfeed for the minimum possible period while corticosteroid pulsed therapy or immunoglobulin therapy is started. After breastfeeding is over, patients may use immunomodulators normally.

**MANAGEMENT AT OUR UNIT**

Since the establishment of the Reference Center for Multiple Sclerosis Litoral Paulista (CEREM Litoral Paulista), on January 2002, as a result of an agreement between the Medical School of the Universidade Metropolitana de Santos (UNIMES) and the DIR XIX of the Secretariat Health of the State Sao Paulo (38), two patients became pregnant and other requested guidance about possible pregnancies. We serve a region along the Sao Paulo state coast between the city of Bertioga and the Parana state border to the South. Currently we have 153 registered patients at our unit, of which 112 are women.

The Neurology Department and the Women’s Health Department, both part of the Medical School of the Universidade Metropolitana de Santos, have strictly followed BCTRIMS and ABN recommendations (14-17), which offer guidelines for the treatment of MS patients that intend to become pregnant or that are already pregnant.

Since the CEREM Litoral Paulista was opened, two MS patients have become pregnant while using immunomodulators. Both were being monitored by neurologists at private offices and were registered at the CEREM Litoral Paulista to receive medication. One of the patients who intended to become pregnant was taking glatiramer acetate prescribed by her neurologist. The other patient wished no further pregnancies, and was using beta interferon, which was changed to glatiramer acetate when the patient became pregnant.
The pregnancy, labor, and puerperium of both patients went uneventful, and the infants were born healthy, with normal weight and height and no malformation.

CONCLUSION

This paper reviews aspects of the intention to become pregnant, pregnancy, labor, and the puerperium in MS patients, based on relevant published papers. We highlight that treatment with immunomodulators is discouraged, and that corticosteroid pulsed therapy is recommended for eventual attacks. Although not encouraged in these patients, breastfeeding is not formally contraindicated.

REFERENCES