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Pregnancy in the context of Multiple Sclerosis

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ABSTRACT

Multiple Sclerosis is a chronic autoimmune neurodegenerative disorder which affects brain, spinal cord and optic nerve. During last years the perception over the disease changed dramatically, now being considered a handleable disease. The particularity of this subject is that Multiple Sclerosis is a disease which affects mostly young women, many of them not having any children at the moment of diagnosis. This article highlights the fact that women diagnosed with Multiple Sclerosis are allowed to get pregnant, and, moreover, they are encouraged to live a normal life. In most cases, disease activity freezes during pregnancy, only a small percentage of women will continue to have clinically and radiologically active disease. For those women, IFN-β and Glatiramer Acetate are the first-choice therapies that should be given. In cases when the disease is not responding to common medication, refractory to treatment forms may be successfully treated with Natalizuab, during the first and the second trimester. Breastfeeding is also encouraged, as it has a protective effect on disease progression. The main purpose of this article is to make a literature review in which to summarize the updates regarding pregnancy and postpartum management, relapses management and, also, the impact of pregnancy on Multiple Sclerosis course. The analysis was limited to articles written in English and published between August 2019 - October 2022 on PubMed, NCBI and Medical Journals.

Keywords: pregnancy, breastfeeding, Multiple Sclerosis, relapses, treatment therapies, immunological tolerance

INTRODUCTION

Multiple Sclerosis is defined as a chronic autoimmune-mediated neurodegenerative disease which affects the brain, spinal cord and optic nerves. The histopathological changes are described as inflammation, demyelination, gliosis and, in the end, axonal damage [1,2,3]. Researchers have found seven types of disease, the most common being the relapsing-remitting form, with an incidence of 80%. Other forms described are: Primary-Progressive (up to 20%), Secondary Progressive, Progressive-Relapsing, Clinically isolated syndrome, fulminant and benign form [4].

Globally, Multiple Sclerosis affects approximately 2 million people, with an incidence of 1:1000 [5] [3]. The first signs of the disease appear between the age of 20 to 40 [5] and the principals risk factors are: Epstein-Bar virus infection, insufficiency of UV radiation exposure, vitamin-D deficiency, vaccinations and genetic predisposition, over which major physical and emotional stressors overlap. The prevalence of the disease is higher among women, they being affected in up to 70% of cases [3].

For a long time, it was believed that pregnancy was dangerous for women with Multiple Sclerosis [1]. Since the end of the last century, after the publi-

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cation of the largest multicultural study (PRIMS), this belief has changed. On the other hand, along with the Disease Modifying Therapies (DMT's) finding, the disease turned from untreatable to a manageable disease. This underlines the importance of pre-conceptional counselling regarding fetal risk after Disease Modifying Therapies exposure and maternal disease progression, and relapses risk in case of medication ceasing. There are many aspects regarding pregnancy which must be clarified, such breastfeeding, loco regional analgesia and the postpartum conduct [6].

METHODES

PubMed, NCBI and Medical Journals were searched for studies written in English regarding the impact of Multiple Sclerosis on pregnant woman and the management of the disease during pregnancy and after childbirth as well. The purpose of this literature review is to synthesize information regarding relapses risk, disease progression, pharmacologic treatment options, way of birth and breastfeeding during pregnancy and postpartum period in women with Multiple Sclerosis.

The literature reviewed was published between August 2019 -April 2022. The publications were selected taking in account the year of publication and the novelty they came with. The keywords used were: Multiple Sclerosis, pregnancy, relapses, disease modifying therapies, immunological tolerance, breastfeeding.

RESULTS

Pregnancy induced immune tolerance and multiple sclerosis

Autoimmune disorders mostly affect women of reproductive age [7]. Intriguingly, women diagnosed with Multiple Sclerosis usually ameliorate during pregnancy. They have equivalent outcomes with the non-pregnant ones who undergo the most powerful available therapies, but with the compromise of a transient postpartum aggravation [8].

During pregnancy the maternal immune system undergoes many changes in order to tolerate the cohabitation and development of a new entity from a genetic point of view [8]. So, pregnancy is a particular immunological condition, wavering between an immune tolerance status and an effective immunity as well [8]. All the immunologic adjustment takes place at the feto-maternal interface. The cell populations involved in this process are dendritic cells, natural killer (NK) cells, macrophages, T-Lymphocytes. Those cells have the capacity to synthesize IL-10, one of the principal cytokines involved in pregnancy immune tolerance [9]. Complement activation suppression [9], decrease production of interferon gamma (IFN-γ), reduced T cell reaction after non-specific stimulation [8], downregulation of metalloproteases and adhesion molecules, reduced antigenic presentation, immunotolerance determined by the presentation of fetal antigens [10] and the shift from a T helper type 1 (Th1) - inflammatory to a T helper type 2 (Th2) anti-inflammatory condition are the most common mechanisms of pregnancy induced immune tolerance [11]. Human chorionic gonadotropin (hCG) is the promoter of the Th2 mediated anti-inflammatory status [11], but Vitamin D is involved as well [12]. Interestingly, in the periphery, T reg lymphocytes, are constantly rising until the second trimester, then will keep steady until childbirth and afterwards will diminish [9]. The influence of pregnancy's hormones and immunological factors may be observed in Figure 1 below.

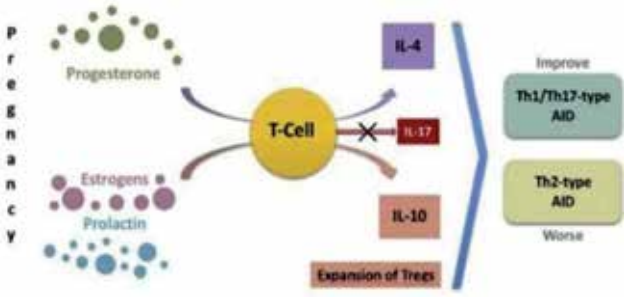

FIGURE 1. The influence of pregnancy's hormones on the progression of autoimmune diseases [12]

All these changes are under the strict control of steroid pregnancy hormones. Androgens generate an anti-inflammatory environment, while estrogens manifest both pro and anti-inflammatory effects. But pregnancy's estrogen concentration is high enough to put down immune responses. Moreover, the increased estradiol level during pregnancy is the principal trigger of immune maternal tolerance [11]. Progesterone has suppressive effects on CD4 T cell activation. It also modulates some genes involved in disease activity, inducing pregnancy immune tolerance as well [8]. The concentration of these hormones increases constantly reaching a peak in the third trimester, yielding the biggest relapse protection [13].

Regarding all from above we can conclude that pregnancy is a physiological disease modifier associated with a considerable decrease in Multiple Sclerosis relapse rate [14].

The impact of pregnancy on multiple sclerosis course

In the last decades perspectives regarding pregnancy in women diagnosed with Multiple Sclerosis have changed. Nowadays, those women are encour-

aged to conceive, especially because the disease had a reduced activity during pregnancy [8]. All the adaptative mechanisms mentioned above are closely controlled by pregnancy steroids. Estradiol, progesterone and androgens promote the switch between Th1 and Th2, with a predominance of Th2 cells. Immediate after delivery, the switch is changed with the predominance of pro-inflammatory Th1 cells, and the modulation is revoked [13]. In addition, the immune system becomes more reactive with a tendency of disorder rebound [15]. Interestingly, pregnancy steroids have not only an anti-inflammatory role, but a neuroprotective one as well [13]. We can conclude that the positive effect of pregnancy on Multiple Sclerosis course is most probably the outcome of immune-endocrine interplay and a decreased maternal immune response [8].

PRIMS, the biggest Multicentre Pregnancy in Multiple Sclerosis Study, revealed a reduction [15] up to 70% [16] in annualized relapse rate (ARR) during the last trimester of pregnancy [15]. The immunomodulatory effect was comparable with the one obtained in patients treated with Natalizumab [10,8]. Unfortunately, the study results showed a higher ARR during the first 90 days postpartum [15] (1.2 relapses/women/year) [8]. Those results are sustained by MRI study. Researchers detected active lesions on MRI T2 sections in the first three months after childbirth [10].

Regarding disease progression, a recent Australian study demonstrated that increased gravidity and parity may decrease the risk of disease onset [2]. But according literature, about 15-30% of patients undergo disease exacerbations during pregnancy [10]. In which concerns disease rebound in the first three months postpartum it seems that Disease Modifying Therapies administered as close as possible to the moment of conception decreases relapses incidence with 45% [3]. Up to 30% of women experience relapses during the first three months postpartum. Sadly, exacerbations experienced during this period seem to be more aggressive and associate higher chances of disability. The presumed risk factors are: exacerbations during pregnancy, a higher EDDS score at the moment of conception, a high incidence of relapses in the last 12 months before conception, relapses after DMT stopping, the use of second line medication [10].

The impact of multiple sclerosis on pregnancy

Multiple Sclerosis is not a hereditary condition, but it associates a genetic predisposition that can be acquired. In general population the incidence of the disease is low (0,1-0,3 %), but in families with a first-degree relative diagnosed with Multiple Sclerosis, the risk can reach up to 2-4 [2]. It seems that this debilitating, neurodegenerative disease, affects the family structure, not just the patient health. Despite Multiple Sclerosis doesn't impair fertility, it appears that women who receive this diagnosis decide to have fewer children [16].

Regarding pregnancy outcome, it seems that these women tend to develop a higher frequency of genitourinary and upper respiratory tract infections during pregnancy [10]. They also associated an increased risk of preterm labour, small for gestational age and malformed new-borns [16,15]. Moreover, these patients complain more often of constipation during pregnancy [15]. According to literature, those patients have a higher rate of operative vaginal delivery [15] and a higher prevalence of Caesarean Section as well (42,4% vs 32,8% in healthy women [6].

MRI monitoring

During pregnancy low-field-strength - MRI (1,5 Tesla) is allowed but, if possible, without contrast [2]. Following the outcome of a large cohort-study, gadolinium in not approved during pregnancy, except in rare cases where it's use is vital for the mother, fetus or both well-being. It seems that the substance can enter via placenta the fetal circulation, and cause nephrogenic systemic fibrosis, stillbirth or neonatal death [10].

Regarding the first large observational MRI study, which took place in a tertiary centre, between 2006-2015, in the first three months postpartum, on Multiple Sclerosis women, were cited following results half of participants had active disease objectified by MRI active lesions in T2 sections or clinical relapses, 25% had both and 15% had just new Gadolinium positive lesions [17]. MRI study made in the postpartum period concluded that despite the presence of new destructive lesions that appeared after delivery the analysed women did not show any cortical atrophy [18]. In contrast, prepartum MRI didn't show any disease activity [17].

Regarding MRI study during breastfeeding, Gadolinium excretion into breast milk and the absorption into the neonate gastro-intestinal tract are <1%. In conclusion, the use of Gadolinium during breastfeeding, is considered safe without needing to interrupt lactation [2].

The images acquired must be analysed in a clinic context because according to one multicentre research can be misinterpreted as Multiple Sclerosis lesions that actually can be sections of migraine, fibromyalgia, neuromyelitis optica and other neurologic conditions [19].

Disease modifyng therapies during pregnancy and postpartum period

Since the beginning of 2000s, due to new Disease Modifying Therapies approval by FDA and EMA, re-

lapsing remitting Multiple Sclerosis became a manageable disease [2]. Despite this, more than 40% of pregnant women with Multiple Sclerosis are not taking any medication in the year preceding conception [3].

Depending on the potency of the immunomodulatory effect, Multiple Sclerosis treatment involves two lines therapies. Regarding first line therapies, EMA approved the use of IFN-β and Glatiramer Acetate during pregnancy for women diagnosed with Clinically Isolated Syndrome and Relapsing-Remitting Multiple Sclerosis. In contrast, patients who were treated with Teriflunomide must stop medication before getting pregnant, moreover, these patients must take Cholestyramine or activated Charcoal until they will reach a Teriflunomide plasma concentration lower than 0.02 mg/L. Due to its short half-life, Dimethyl Fumarate can be administered until conception [20].

Second line therapies, such Fingolimod, Siponimod, Ozanimod and Cladribine, must be stopped before conception, furthermore in case of fetal exposure an ultrasound must be immediately performed [20].

Natalizumab is the most potent second line Disease Modifying Therapy approved during pregnancy and not only. Since 2019, the Association of British Neurologists [10], recommend maintaining Natalizumab therapy until 34 weeks of pregnancy. Because the relapses normally resume after 12-16 weeks from last dosage, the guidelines recommend resuming treatment at 8-12 weeks after the last shot [18]. These women must perform monthly blood and urine tests, including John Cunningham virus serology [20]. Regarding the new-borns from mothers treated with Natalizumab during pregnancy, immediately after delivery a thrombocytopenia and anaemia screening must be performed [18].

Because they are recently introduced in Multiple Sclerosis treatment guidelines, information about the neonatal outcome after Ocrelizumab and Rituximab exposure are lacking, therefore the use of these Anti-CD20 monoclonal antibodies is not recommended [18] moreover they must be stopped before conception. FDA recommendation is that last infusion of Ocrelizumab to be with at least 6 months before conception and 1 month for Rituximab [20]. Regarding Alemtuzumab, literature cites many cases of fetal autoimmune thyroiditis, premature birth and neurocognitive deficiency. Guidelines recommendations are to stop treatment at least 1 month before conceiving [10].

Although pregnancy is considered a physiological immunomodulatory state, some patients manifest relapses during pregnancy. In the second and third trimester of pregnancy, the first choice treatment is 1000 mg of Methylprednisolone administered daily for 3-5 days. Methylprednisolone is inactivated by the 11-β-hydroxysteroid dehydrogenase, while Dexamethasone and Betamethasone cross the placental barrier and enter into fetal circulation [6]. Corticosteroids exposure during first pregnancy trimester was associated with teratogenicity such as orofacial cleft, low birth weight, gestational diabetes, neurodevelopment impairment [15] and miscarriage, therefore, they are not recommended [6]. Although there are few statistical data, plasma exchange can be considered an alternative for corticosteroids, in case of first trimester relapses [15].

In case of fetal exposure to corticosteroids or Disease Modifying Therapies, a detailed fetal ultrasound must be performed at 20-22 weeks of gestation [20]. Also, vitamin D supplementation should not be discontinued during pregnancy. Multiple Sclerosis pregnant women can take up to 4000 IU of vitamin D3, targeting the upper half of the reference interval [15].

During pregnancy, Multiple Sclerosis treatment must be individualised according to disease type, patient's age, disability degree, clinical and radiological disease activity, past relapses frequency and risk benefit ratio [18].

BREASTFEED AND ANESTESHIA

Women diagnosed with Multiple Sclerosis are allowed to breastfeed, moreover exclusive breastfeeding decreases the risk of disease exacerbation with 43% [10]. It has to be mentioned that the protective effect against relapses is limited at the first 6 months after delivery; another condition is that that woman to exclusive breastfeed [20].

In which concerns the passage of Disease Modifying Therapies molecules in breastmilk, IFN-b and GA are large molecules who cannot pass, so their administration is considered safe during breastfeeding [10]. Besides, according to literature, if they are administered in the first 3 months postpartum, the relapsing risk is reduced by half and the global risk of relapses decreases for at least 1 year after delivery [2].

Regarding second line therapies, deeper research must be done, in order to clarify if Ocrelizumab and Natalizumab are safe for the infant [10]. Until then, women with high disease activity must restart Multiple Sclerosis treatment immediate after delivery [15]. In case of postpartum relapses, the patient must postpone with 2-4 h breastfeeding, because Methylprednisolone usually passes into breastmilk [20].

Regarding way of birth, vaginal birth is not contraindicated in women with Multiple Sclerosis. Women with spasticity, during labour, can be managed by administration of benzodiazepines or epi-

dural analgesia. A little more attention must be payed to women with spinal cord lesions because they may not feel uterine contractions, especially those who have lesions localized under T11 [3].

CONCLUSIONS

Multiple Sclerosis is a neurodegenerative autoimmune disease which usually affects women at reproductive age. Over the last decades, the view over the disease course suffered many changes; it turned from an untreatable disease to a manageable one, especially due to new therapies approved in the last years by FDA and EMA. These findings improved life quality for women diagnosed with Multiple Sclerosis. Also, the implementation of Disease Modifying Therapies created the opportunity for these women to live a normal life, including the possibility of having children. Moreover, these women are encouraged to conceive. Although pregnancy and breastfeeding are considered protective against Multiple Sclerosis relapses, Methylprednisolone seems to be a safe therapy option during the second and the last trimester. During pregnancy women with more aggressive disease forms can be successfully treated with IFN-β, Glatiramer Acetate and Natalizumab. Multiple Sclerosis research is progressing with an astonishing speed, furthermore in the last years the progress was impressive. There is a lot of research that must be done, but certainly in a few decades Multiple Sclerosis will turn from a manageable disease into a treatable one.

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