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Pregnancy in Multiple Sclerosis: A Portuguese cohort study

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ABSTRACT

Background: Pregnancy in Multiple Sclerosis (MS) has been a controversial issue, without international standardized treatment recommendations. The goal of our study was to evaluate the clinical course of MS during pregnancy and the respective therapeutic options, obstetrical outcomes and breastfeeding data.

Methods: This was a retrospective study including women with a diagnosis of relapsing-remitting MS at least one year before pregnancy. Three periods were evaluated: one year prior to pregnancy, pregnancy and one year postpartum. Information acquired included demographic and disease activity data, treatment options, and obstetrical and breastfeeding data.

Results: From a cohort of 1134 patients and 777 women, we included 127 pregnancies in 97 women (111 deliveries of a live infant, 11 spontaneous abortions, 3 fetal deaths and 2 voluntary abortions). The annualized relapse rate (ARR) decreased during pregnancy, mainly in the third trimester (prior to pregnancy 0.6 ± 0.8 vs. during pregnancy 0.3 ± 0.6, $p = 0.006$). There were no significant changes in the ARR in the year after delivery compared to baseline (0.6 ± 0.8 vs. 0.6 ± 0.8, $p = 0.895$). Patients with relapses in the postpartum period had a shorter disease duration at conception (5.4 ± 3.9 vs. 7.4 ± 4.7; $p = 0.029$) and breastfed less (53.5% vs. 72.1%, $p = 0.046$). In the multivariate analysis, relapses during pregnancy predicted postpartum relapses (OR = 4.9, $p < 0.005$). Neither the previous use of disease modifying therapy (DMT), given to 80.2% of women, nor breastfeeding, caesarean delivery (CD) or epidural analgesia (EA) had an impact on the presence of postpartum relapses. Compared to baseline, the Expanded Disability Status Scale (EDSS) increased in pregnancy and the postpartum period (1.6 ± 0.7 vs. 1.7 ± 0.9 vs. 2.1 ± 1.0, $p < 0.001$). CD was performed in 43.3% of patients, mainly because of fetal-pelvic incompatibility (35.7%) and EA was performed in 63.9%. The most frequent complications were restriction of fetal growth (4.5%) and gestational diabetes mellitus (3.6%). Concerning newborns, 6.4% had birth asphyxia and 6.1% low birth weight. No malformations were registered.

Conclusion: Despite a reduction in the relapse rate during pregnancy, the presence of relapses during pregnancy predicted postpartum relapses, with impact on disability. DMT appeared to have no influence on clinical or obstetrical outcome. MS did not have a deleterious effect on the pregnancy course. CD and EA were safe procedures, with a tendency towards CD in MS patients, compared to Portuguese women in general. Breastfeeding did not influence MS activity.

1. Introduction

MS affects young women of childbearing age (Confavreux, 2004; Hellwig, 2014). In PRIMS, the relapse rate decreased during pregnancy, with a rebound during the first three months postpartum (Confavreux et al., 1998). The underlying mechanism is based on a decrease in cellular immunity and an increase in humoral immunity, with a shift from Th1 to Th2 responses during pregnancy, which is reversed after delivery (Confavreux et al., 1998; Vukusic and Confavreux, 2006). In determining which factors predict an increase in postpartum disease activity, some studies have highlighted the influence of an increased relapse rate in the pre-pregnancy year and pregnancy, and a higher

Abbreviations: MS, Multiple Sclerosis; PRIMS, Pregnancy In Multiple Sclerosis; EDSS, Expanded Disability Status Scale; DMT, disease modifying therapy; IVIg, intravenous immunoglobulin; GA, glatiramer acetate; INF, interferon; IM, intramuscular; EA, epidural analgesia; CD, caesarean delivery; VD, vaginal delivery; WHO, World Health Organization; SA, spontaneous abortion; FD, fetal death; BA, birth asphyxia; BW, birth weight; ARR, annualized relapse rate

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EDSS score at pregnancy onset (Hellwig, 2014; Portaccio et al., 2011; Vukusic et al., 2004). Importantly, pregnancy appears to have no influence on the progression of disability in MS (Confavreux et al., 1998; Hellwig, 2014; Hughes et al., 2014; Vukusic and Confavreux, 2006). However, questions about the type and severity of relapses during this period remain to be answered.

Multiple studies have looked at ways of reducing the risk of postpartum relapses as no international standardized treatment recommendations are defined, but no definitive evidence exists that any option is truly effective (Fabian, 2016; Hellwig, 2014). Current recommendations for pregnancy management in MS are that women intending to get pregnant should consider DMT discontinuation to prevent potential fetal harm (Hutchinson, 2011; Vukusic and Marignier, 2015). However, these recommendations are based on expert opinion due to the absence of controlled data on the risks of drug treatment (Fragoso et al., 2013; Hutchinson, 2011). The FDA classification for MS immunomodulatory drugs specifies that there are no safe Class A drugs (Fabian, 2016; Vukusic and Marignier, 2015). IVIg use in pregnancy is also non-consensual regarding efficacy and safety (Achiron et al., 2004; Haas, 2000).

Issues of pregnancy outcome, delivery and breastfeeding in MS are receiving renewed interest (Fabian, 2016; Hellwig, 2014). A few studies have addressed the safety of EA and CD, showing that these procedures have no impact on MS activity (Pasto et al., 2012; Vukusic and Confavreux, 2006; Vukusic et al., 2004). Data regarding breastfeeding is still controversial, with doubts about a possible protective effect remaining (Airas et al., 2010; Hellwig et al., 2015; Portaccio et al., 2011).

With this study we aimed to evaluate the clinical course of MS during pregnancy and the respective therapeutic options, obstetrical outcomes and breastfeeding data.

2. Methods

2.1. Participants

The study included pregnancies in women who had the diagnosis of relapsing-remitting MS according to the McDonald Criteria 2010 (Polman et al., 2011) for at least 1 year before conception. To assess the impact of pregnancy on MS activity, we only considered pregnancies resulting in deliveries of a live infant.

Data from 1993 to 2015 were collected retrospectively by consulting the clinical process and by telephone assessment, considering the period of 1-year pre-pregnancy, pregnancy and a 1-year postpartum follow-up. Demographic data, the annualized relapse rate and type of relapse, as well as disability and treatment options were assessed. Pregnancy complications, mode of delivery (vaginal or caesarean), epidural anaesthesia, outcome of newborns and breastfeeding were also evaluated.

2.2. Concepts and definitions

A relapse was defined as the appearance or reappearance of one or more symptoms attributable to MS, accompanied by objective deterioration as shown by neurological examination, lasting at least 24 h, in the absence of fever and preceded by neurological stability for at least 30 days (Polman et al., 2011). Disability was assessed using the EDSS (Kurtzke, 1998) and progression defined as a 1.5 point EDSS increase from a baseline score of 0; 1 point EDSS increase from baseline scores of 1–5.5; and 0.5 point EDSS increase from baseline scores > 5.5, sustained for six months (Pasto et al., 2012).

Following the WHO's definition, we included in the breastfeeding group those who predominantly breastfed (the infant received breast milk only, with liquid supplementation allowed) and those who supplemented this with complementary feeding (the infant received breast milk, with liquid and food supplementation allowed, including non-human milk), as opposed to those not breastfeeding at all (the infant did not receive any breast milk)(WHO, 1996).

Data on the type of delivery were categorized into VD, with assistance (use of forceps or ventouse) or without, and CD; information on EA administration was included.

Other outcomes were defined as follows: SA - fetal loss before 22 completed gestational weeks; FD - fetal loss ≥ 22 gestational weeks or fetal weight of ≥ 500 g; BA - 5-min APGAR score of under 7 (0−10); low BW-less than 2500 g (WHO, 2004).

2.3. Statistical analysis

Baseline characteristics were reported as frequency (%) and mean ± SD. The ARR was calculated in the year before pregnancy, during pregnancy and in the year after delivery. Comparisons between groups were performed with the Chi-square test (differences between categorical variables), Student's *t*-test (continuous variables when normally distributed), and Mann-Whitney *U* test (non-normally distributed continuous variables) when appropriate. For matched samples the Wilcoxon test was used. Clinical factors likely to predict a relapse after delivery were analysed by logistic regression analysis. P values < 0.05 were considered statistically significant.

2.4. Ethics

All patients gave their written informed consent for study participation. The study was approved by the local ethics committee.

3. Results

From a cohort of 1334 patients and 777 women followed up in our MS outpatient department, 97 women were included in this study with a total of 127 pregnancies. 111 pregnancies resulted in the delivery of a live infant. Mean pregnancy duration was 39.0 ± 1.7 weeks and 18.2% of the women had had a previous pregnancy. Table 1 shows the main demographic and clinical characteristics of the study cohort.

3.1. Disease activity

The overall ARR in the year before conception, with 80.2% of women on DMT, was 0.6 ± 0.8% and 41.3% of patients had a relapse during that year. The mean EDSS was 1.6 ± 0.7.

During pregnancy, 17.2% of the patients had relapses, mainly in the first trimester (9.9%), with sensitive and spinal cord relapses being the most frequent subtypes. The ARR during pregnancy was 0.3 ± 0.6 with a mean EDSS of 1.7 ± 0.9. There were significant changes in the ARR

Table 1
Characteristics of the study cohort.

Variables	Total
Age at conception, y, mean ± SD	31.9 ± 4.9
Age at disease onset, y, mean ± SD	25.6 ± 5.7
Disease duration at conception, y, mean ± SD	4.9 ± 2.7
Before Pregnancy (1 year)	
Annualized relapse rate, mean ± SD	0.6 ± 0.8
EDSS prior to conception, mean ± SD	1.6 ± 0.7
DMT prior to pregnancy, n (%)	89 (80.2%)
Pregnancy and Delivery	
Annualized relapse rate, mean ± SD	0.3 ± 0.6
EDSS during pregnancy, mean ± SD	1.7 ± 0.9
Epidural Analgesia, n (%)	62 (63.9%)
Caesarean Delivery, n (%)	42 (43.3%)
Postpartum period (1 year)	
Annualized relapse rate, mean ± SD	0.6 ± 0.8
EDSS in postpartum period, mean ± SD	2.1 ± 1.0
Breastfeeding, n (%)	72 (64.9%)

Abbreviation: y, years; SD, Standard Deviation; EDSS, Expanded Disability Status Scale; DMT, disease-modifying therapy.

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