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The effects of long-term exposure to disease-modifying drugs during pregnancy in multiple sclerosis

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ABSTRACT

Background and objective: Women with multiple sclerosis (MS) who intend to get pregnant are often advised to discontinue disease modifying therapy (DMT) prior to conception. This recommendation is not based on medical evidence and may interfere with disease control by immunomodulatory drugs. The present study was designed to help discuss the effect of DMT for MS on pregnancy and on disease course.

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Patients and methods: Retrospective data from 152 pregnancies of 132 women with MS were collected by the physician in charge of the case. All data were entered into a specific file for qualitative and quantitative statistical analysis.
Results: From the total group of patients, 89 pregnancies occurred without any exposure to MS drugs, while 61 pregnancies occurred with at least eight weeks of exposure to MS immunomodulatory drugs. The rate of obstetric and neonatal complications was similar in both groups, except for the newborn weight and height which was smaller for mothers receiving medications. Mothers' post-delivery relapse rate and EDSS scores in the follow-up period were significantly higher in the absence of treatment.
Conclusion: It is possible that, with further such supportive data, international guidelines on MS treatment in young women who intend to get pregnant may need to be revised.

1. Introduction

Women who intend to get pregnant are often advised to discontinue disease modifying therapy (DMT) for Multiple Sclerosis (MS) prior to conception, as well as during gestation and breastfeeding. These recommendations are present in all international MS guidelines that cover the subject of pregnancy and MS, usually in a short paragraph and without a scientifically based rationale [1]. This continues to occur at a time when tolerance to disease activity is reaching unprecedentedly low levels, when "freedom from disease activity" is becoming a measure of successful treatment [2,3], and when combined clinical and radiological parameters are being used to assess disease activity in place of annualized relapse rate.

Women of childbearing age are the most representative population of MS patients, and pregnancy is known not to affect the short-term or long-term MS disease course or impact the offspring, other than the inherent increased MS risk in first degree relatives [4,5]. Clinical practice has already significantly evolved from a position where women with MS were advised not to become pregnant or to consider termination if exposed to any MS drugs. In fact, the evolving management of pregnancy in MS seems to be similar to that of pregnancy in epilepsy which has progressed from a time when pregnancy was discouraged to the present, where knowledge of the effects of the disease and drug treatment enables evidence based recommendations [6].

Women with MS who intend to get pregnant and stop treatment are at risk of worsening their disease and compromising motherhood itself. Furthermore, women may get pregnant while using DMT and, along with their doctors, have little knowledge of the potential risks to pregnancy and the baby. Considering the fact that no prospective, randomized, double-blind clinical trial will ever be carried out for DMT in pregnancy, the best evidence-based data can only be achieved by observational studies [6]. Moreover, although pharmaceutical companies have pharmacovigilance departments dealing with pregnancy during the use of drugs, they do not open their databases for scientific and unbiased evaluation.

Only very recently has evidence of little to no harm for first-line DMT to offspring been discussed in relation to MS and pregnancy [7–11]. With detailed and methodologically sound studies, some groups have published their results, which may eventually be reflected in newer treatment guidelines for MS.

The present work was designed to help discuss what is known, what is best and what we can tell patients with MS who intend to become (or already are) pregnant, regarding DMT. The objective was to analyze the potential effects of long-term exposure to DMT during pregnancy as well as to observe whether these might influence obstetric and MS outcomes. This study was set up as an open and internationally-based attempt to create a database for studying exposure to DMT during pregnancy. Several colleagues from different countries were contacted and the initial results presented here include data from four countries. This study was carried out without financial support for any of the authors; none of the researchers are or were employed by any pharmaceutical company.

2. Patients and methods

The Ethics Committee approvals for this study were regional and institutional. Each author was responsible for obtaining approval in accordance with the rules and regulations of their own country. Patient confidentiality was guaranteed at all times, and will remain in place after this publication.

An Excel datasheet asking for demographic, clinical, obstetric and neonatal information relating to patients and their offspring was sent to doctors who were willing to participate in the study. Patients were included if they had at least one pregnancy with complete data after MS had been diagnosed according to the revised McDonald criteria 2010 and if they belonged to one of the following two groups: (1) no exposure to any DMT for a minimum of three months prior to pregnancy; (2) a minimum of eight weeks of continuous exposure to any DMT at the start of pregnancy. The first group, without drug exposure, was considered to be the "control group". The second group, considered to be the "drug exposure group", would include data from the time the child was most susceptible to the effects of drugs, i.e. conception and the subsequent eight weeks.

Data collection was retrospective, using patients' medical records. Whenever data were missing from the medical records, the physician in charge of the case contacted the patient in order to obtain missing details. Only patients actually seen by the authors of this study were included.

The author analyzing the database did not participate in the collection of data and performed the analysis blindly to the aims of the study. Data were analyzed using GraphPad Prism version 5.04. Continuous variables were analyzed by means of the paired and the unpaired Student's t-test and one-way ANOVA with Tukey post hoc testing. Categorical data were assessed by means of odds ratios.

3. Results

Four countries entered patients into the study: Brazil, United Kingdom, Mexico and Argentina. Data from 152 pregnancies in 132 women with MS were collected; 89 pregnancies occurred without exposure to DMT during pregnancy and 61 pregnancies occurred with at least eight weeks of exposure (41 to glatiramer acetate [GA], 17 to interferon [IFN], two to pulses of immunoglobulin and one to high-dose oral corticosteroids). The mean duration of drug exposure during pregnancy was 18.4 ± 13.2 weeks (range = 8–40 weeks). Demographic and clinical parameters of these groups are shown in Table 1. Comparing the "no drug exposure" and "at least eight weeks of drug exposure" groups of patients, there were no significant differences between the groups with regard to current age, age at the time of initial symptoms of MS, age at the time of MS diagnosis,