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Time to Pregnancy in Multiple Sclerosis: A Case-Control Study

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Abstract

Multiple sclerosis (MS) is the most common degenerative neurologic disorder in young adults, with a female predominance. A couple's fertility is inherently uncertain. Time to Pregnancy (TTP) refers to the number of menstrual cycles exposed to unprotected intercourse until conception. In normal couples, the cumulative pregnancy rate after 6 months is near 75%. With increasing TTP, there is an important decline in conception rate per cycle. In MS, TTP can be used to a better birth planning regarding pharmacotherapy.

Methods: Case-control, longitudinal study. Pregnancies between 2007-2016 was included. Demographical data and clinical characteristics of MS patients were analyzed by medical records and patients interview.

Results: 54MS patients and 64 controls were included consecutively. No differences in demographical data were found, except for a higher proportion of primiparous in the control group. We found no differences in TTP between groups. The majority of pregnancies occur during the first 6 months (75%).

Discussion: None of the DMT is approved during pregnancy, and some need a mandatory washout period, to avoid fetal harm. The washout period entails the risk of MS reactivation. We found no significant difference in TTP between MS patients and controls, occurring the majority of the pregnancies during the first six months. These results further suggest that there is no direct impact of MS on fecundity when comparing to healthy age-matched women. In MS patients, knowing the usual TTP could be important, because there is an increased risk of relapse in those patients where the DMT were withdrawn.

Keywords: Multiple sclerosis; Pregnancy; Time to pregnancy; DMT; Washout period

Introduction

Multiple sclerosis (MS) is the most common degenerative neurologic disorder in young adults, with at least 2.5 million individuals affected worldwide. The disease shows a female predominance that now approximates 3 to 1. Nowadays, pharmacotherapy is probably one of the most important issues regarding pregnancy in MS [1]. Fecundity refers to the biological ability to give birth. It is estimated for a population by the Time to Pregnancy (TTP), which refers to the number of menstrual cycles exposed to unprotected intercourse until conception. In normal couples, the fecundity, or the chance to achieve a pregnancy within one cycle, is 20% [2,3]. While the process of attempted conception over time can be modeled as occurring in continuous time, it has been proposed to model the process as one that occurs over successive discrete menstrual cycles [4]. This is because most of the pregnancies occur within the first six menstrual cycles. In fact, in normal fertile couples, the cumulative pregnancy rate after 6 months ranges from 75 to 90% [2,5,6]. A TTP of 12 months or more is often used as a measure of sub fecundity [7]. TTP estimations are important to find suitable thresholds to determine the prevalence of subfertility. These thresholds are used as the major indicator for timing routine infertility investigations and eventually starting treatment [5]. In MS, TTP can be used to a better birth planning regarding pharmacotherapy. Nowadays there are distinct approved disease-modifying therapies (DMT) for relapsing forms of MS, which encompass many different mechanisms of action. None of the DMTs are approved for use in women who are actively trying to become pregnant and most of them are not recommended for use in patients who are pregnant or trying to become pregnant. In addition, none of the DMTs are approved during lactation. The use of DMT before pregnancy is now common in many MS patients, and it has been suggested that its use might affect postpartum relapses incidence [8,9]. A study, using the MS Base global registry, reported that prior DMT use, any time in the 2 years before pregnancy, resulted in a 45% decreased risk for postpartum relapse [10]. Our aim is to analyze TTP in an MS cohort and to compare their results with healthy age-matched controls. Knowing the usual TTP in MS could help us planning an appropriate personalized strategy, which may include an adequate DMT washout period to minimize the risk of a relapse rebound and to avoid iatrogenic harm.

Material and Methods

We conducted a retrospective case-control, longitudinal study. Patients with diagnosis of MS admitted at the Hospital General Universitario Gregorio Marañón of Madrid, Spain, who have had a pregnancy between2007 to 2016, have been included [11]. MS diagnosis was based on the McDonald criteria and the 2010 revisions to these criteria, depending on the date of diagnosis [12].

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Table 1: Demographical data.

	MS group (54 patients)	Control (64 patients)	P value
Age at conception	32.7 YO (SD 4,3)	34,8 YO (SD 4,8)	>0.05
Prior pregnancies	Primiparous 10 (18.5 %) Multiparous 44 (81.5 %)	Primiparous 27 (42.1 %) Multiparous 37 (57.9 %)	0.02
Abortions	1 previous abortion: 14 (26%) ≥2 previous abortions: 3 (5%)	1 previous abortion: 13 (20%) ≥2 previous abortions 2 (3%)	>0.05
Unplanned pregnancy	9 (16.6 %)	8 (12.5%)	>0.05
Infertility diagnosis work up	10 (18.5 %)	12 (18.7 %)	>0.05

All patients were evaluated at our MS clinic once pregnancy was confirmed. Neurological assessments were conducted every 3 months during pregnancy and at 3 months after delivery. During this period, patients were evaluated for the appearance of any worsening in their neurological status, suggestive of relapse or disease progression. Besides, they were instructed to report any symptoms that could arise in between the scheduled visits. The appearance, reappearance or worsening of focal neurological signs lasting more than 24 hours in the absence of fever was regarded as a relapse. Demographical data and clinical characteristics of MS patients were collected from their medical files, and gathered the following data: maternal age at conception, clinical form of MS, disease progression in years, annualized relapse rate (ARR)2 years prior conception, the degree of disability according to the Kurtz ke EDSS, and history of pharmacological treatment [13]. All neurologists with Neurostatus e-Test certification performed the neurological examination on each visit [14]. Reproductive history and potential confounders were also analyzed by medical records or using self-questionnaires that were completed during the outpatient appointment and included the number of prior pregnancies, prior live births and if the pregnancy was planned. Time to Pregnancy was assessed by a retrospective recall. The control group was randomly selected from among all pregnant women attended at our institution during the study period. All participants were attended by the hospital's gynecology department and received the standard prenatal and postnatal care. All patients were informed and approved to participate in this study prior inclusion. Each patient signed an informed consent form for participation in the study. Our hospital ethical committee approved the realization of this study. Continuous variables were expressed as either means ± SD or means and ranges. Normal distribution was assessed with the Kolmogorov-Smirnov test. To compare means between 2 groups, we used parametric (*t*-test) and non-parametric tests (Mann-Whitney *U* test), depending on whether or not data was normally distributed and on the total number of patients of each group. TTP was recorded as months, and its distribution was described as the cumulative proportion of pregnancies occurring up to a given waiting time. Statistical analysis was conducted using SPSS version 21.0 and statistical significance was set at $p < 0.05$.

Results

Fifty-four women with MS were included consecutively and 64 controls. Demographical data and reproductive history of the MS patients and the controls group are shown in (Table 1). No differences in the general demographical data were found between both groups, except for the proportion of primiparous, being higher in the control group (p 0.02), which might reflect that the MS patients prefer to start earlier their reproductive life planning. The clinical characteristics of the MS group are shown in (Table 1 and 2). Twenty seven (50%) MS patients were treated with DMT prior pregnancy, most of them with Interferon Beta formulations. Eight (14.8%) patients were treated with subcutaneous Interferon Beta-1a, 6 (11%) with intramuscular Interferon Beta-1a, 5 (9%) with Interferon Beta-1b, 6 (11%) with Glatiramer Acetate, 1(2%) with Fingolimod and 1 (2%) with Natalizumab. Mean time on DMT was of 20 months (range 2-130 months). All MS patients who had a planned pregnancy underwent a controlled wash out strategy, depending on which DMT they were on. They were instructed to wait at least 1 menstrual cycle until start conception in all DMT cases, except the patient on Fingolimod, who completed a wash out period of 2 cycles. After the treatment withdrawn, the mean delay until having a positive pregnancy test was of 3 months (range 1-24 months). Nine (16%) MS patients presented an unplanned pregnancy during DMT treatment, being 3 (5%) patient sunder Glatiramer acetate, 2 (4%) on subcutaneous Interferon Beta-1a, 2 (4%) on intramuscular Interferon Beta-1a, 1 (2%) on Interferon Beta-1b and 1 (2%) on Natalizumab. No serious adverse effects were reported in any of their 9 cases. Their pregnancies developed without complications, deliveries were normal and newborns were healthy. After analyzing the TTP in MS patients and the control groups with the Kolmogorov-Smirnov test, we found that the parameters have a not normally distribution, so we used the Mann-Whitney U test for comparing them. We found no differences in TTP between both groups. The majority of pregnancies occur during the first 6 months (70-75%), as it is shown by the cumulative distribution of TTP (Table 3).

Table 2: Clinical characteristics of the MS group.

	MS group (54 patients)
Clinical form of MS	50 (92,5%)RRMS 3 (5.5%) PRMS 1 (2%) PPMS
Disease evolution (years)	9 YO (SD 5,2)
EDSS at pregnancy	0.7 (range 0-6)
ARR 2 years before pregnancy	0.4 (range 0-1,5)
Nº of treated patients with DMT prior pregnancy	27 (50%)

Discussion

Our study showed that there is no significant difference in TTP between MS patients and controls, with up to 70% of pregnancies occurring during the first six months. These results further suggest that there is no direct impact of MS on fecundity when comparing to healthy age-matched women. Human reproduction is a matter of chance depending on sequential processes that may lead to a pregnancy and to the birth of a healthy child. These processes include oogenesis and spermatogenesis, sexual intercourse and

Table 3: Time to pregnancy.

TTP	MS patients (54)	Control group (64)	P value
≤3° months	34 (62.9%)	39 (60.9%)	>0.05
≤6° months	38 (70.3%)	48 (75%)	>0.05
≤12 months	48 (88.8%)	51 (80%)	>0.05
≤24 months	54 (100%)	64 (100%)	>0.05

transport of gametes, fertilization, and migration of the embryo to the uterus and its subsequent implantation, and finally intrauterine tolerance and development of the fetus [15]. A couple's fertility is inherently uncertain [4]. Empirical models to predict a couple's chance of conceiving spontaneously are complex and may include the duration of non-conception, female age, previous fertility status and percentage of motile sperm [4]. With age, cumulative probabilities of conception decline because of heterogeneity in fecundity increases due to a higher proportion of infertile couple [5]. The duration of infertility, or TTP, is usually used as a major factor for timing routine exploration and infertility treatment. Prospective population-based studies demonstrated that the TTP in most women is not longer than 6 months [3]. Considering the influence of extreme scores, Mean value in TTP might not be the best way to accurately reflect the typical delay in conceiving a pregnancy. Despite this, in a French study analyzing TTP in a multiple sclerosis cohort, they found an average of 7.53 months [17]. Another study demonstrates substantial variations in fecundity between different European centers, as estimated by the monthly TTP distribution. In that study, the French center had the longest TTP and Southern Italy the shortest [7]. With increasing TTP there is an important decline in conception rate per cycle, so it has been proposed to raised the question of subfertility after six cycles of unprotected intercourse without conception, and not to wait until the 12 months [5]. In MS, knowing the usual TTP could be an important factor to take into consideration for the management of female patients when planning a pregnancy. For a personalized planning strategy, in addition to TTP, it must be considered the disease activity, disability status, personal preferences and the patient's risk tolerance. One of the most important decisions the neurologist must face is whether treatment should be discontinued, maintained, or changed by another one that has a better side effects profile. The decision must be balanced against the risk of relapse in those patients were the DMT is withdrawn, or the eventual risk of fetal harm when maintaining it [6].

DMT washout periods

None of the DMTs are approved during pregnancy, and some of them need a mandatory washout period, to avoid any possible interference with the fetal development. According to this, a controlled washout period is sometimes required, to prevent an MS reactivation and not to interfere with conception [18,19]. The DMT washout period should be as short as possible. One consensus group proposed monthly pulsed corticosteroids until pregnancy is achieved in very active MS women or those with a history of delayed conception [20]. In 1979, the FDA established five letter risk categories-A, B, C, D or X - to indicate the potential of a drug to cause birth defects if used during pregnancy, based on what was known from human and animal data. In 2015, the FDA replaced the former pregnancy risk letter categories on prescription and biological drug labeling with a narrative risk summary based on available data. Prescription drugs and biologic products approved after June 2015 now have the new labeling information. Previously approved prescription products may have to progressively incorporate the labeling changes in the near future. The Interferon Beta (IFNb) and Glatiramer Acetate (GA) have been the first-line treatment for MS for more than 2 decades, so they have the largest accumulated pregnancy exposures registries and global safety databases. The IFNb are pregnancy category C. Some reports suggest human maternal IFNb exposure is associated with lower infant birth weights and length, and a higher incidence of premature births, but other analyses do not confirm these findings [20,21]. The problem is that they have shown dose-dependent first-trimester abort effects in primate models at 2.8 to 40 times the recommended human dose [1]. GA is pregnancy category B, the best pregnancy rating among the DMTs. It does not cross the placental barrier and has not been associated with negative pregnancy effects in either animal or human studies [20]. Teriflunomide has the most profound warning, being X category. It shows selected teratogenic and embryo lethal effects in multiple animal species, at doses below those used clinically. When necessary, there is a rapid elimination protocol (using oral cholestyramine over several days) to quickly lower Teriflunomide levels to less than 0.02 μg/ml; otherwise, it can persist in the body for up to 2 years. Fingolimod, pregnancy category C, is teratogenic in rats, and it is associated with fetal malformations, death and growth retardation in rabbit and rat models. When treatment is stopped, elimination of Fingolimod takes approximately two months, so the recommended washout period is 2 months. Dimethyl fumarate is pregnancy category C. Not reported malformations in humans to date. In rats, it is associated with embryotoxicity and teratogenicity, with malformations observed in organs, coccyx and skull bones, at doses two times higher than the approved human dose. Based on its short half-life, there is an author opinion that a washout period is probably not necessary [1].

Natalizumab, pregnancy category C, has been used during human pregnancies without notable teratogenicity, but newborns may experience transient hematologic abnormalities including anemia and thrombocytopenia. In guinea pigs, it has been associated with decreased pup survival at 7 times the human dose, and in primates with reversible fetal hematologic abnormalities, at doses 2.3 times the human dose. When planning a pregnancy in patients on Natalizumab, washout should be as short as possible to avoid MS reactivation, with recommendations ranging from 1 to 3 months. A recent report suggested one could justify no washout since monoclonal antibodies do not cross the placenta until the second trimester, so the teratogenic risk is unlikely [22]. The rationale is based on that IgG is the only antibody isotype to significantly cross the placenta, and this transfer does not start until week 13, and peaks in the third trimester [23]. Alemtuzumab is pregnancy category C. It is embryo lethal in mice, and can lower offspring lymphocyte count. There is a higher risk of hypothyroidism and neonatal Graves' disease with thyroid storm. The recommended washout period is 4 month.

Mitoxantrone, pregnancy category D, is associated with growth retardation and premature delivery in animal models, and there is one case of Pierre Robin syndrome in human exposures. It is recommended a 6 months washout period before pregnancy. For the pregnant MS patient, the appropriate counseling remains that the preferred option is not to use any DMT. However, GA, and to

a lesser extent IFNb, have been used during pregnancy for women in whom there is concern about extended treatment-free periods [24-26]. Based on this, there is increasing consensus that GA and the IFNb do not require washouts, and can be continued until pregnancy is confirmed, but definitive data is lacking [1]. The limitations of this study are related to been a single-center study. Recall bias must be considered as well. Recall bias interpretation of the TTP distribution in a pregnancy-based study is complex since the pregnancy-based TTP distribution is conditional on a pregnancy actually occurring [7]. At long-term recall, TTP may sometimes only be roughly estimated [27]. However, it has been published that, in this area, data can be satisfactorily derived retrospectively by using a short questionnaire [28]. Infertile couples were excluded from our study, and we did not consider all the different issues related to subfertility, such body mass index, smoking habits, intercourse frequency or the different fertility conditions commonly associated with infertility such as low sperm counts or pelvic pathology.

Conclusion

This study showed that there is no significant difference in TTP between MS patients and controls, occurring majority of the pregnancies during the first six months. In those couples where a prolonged TTP would be expected, based on their previous reproductive history, female age and obstetrics comorbid status, a preventive treatment until conception could be necessary [29]. Glatiramer Acetate and IFNb seem to be a feasible option during the TTP, but definitive data is lacking. More research is needed to establish the best strategy when an MS patient decides to conceive a pregnancy.

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