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Definitive childlessness in women with multiple sclerosis: a multicenter study

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Abstract:	OBJECTIVES The frequency of definitive childlessness in women with Multiple Sclerosis (MS) may be higher than in the general population. MS may also affect decisions on the delivery procedure and on breast-feeding issues. Aim of the study was to assess: the frequency of childlessness and its possible causes, the proportion of cesarean deliveries (CD), and the frequency of breast-feeding in patients and controls who have reached the end of their reproductive period. METHODS Female MS patients (>43 years) and controls (>45 years) filled-out a questionnaire. RESULTS We enrolled 303 patients and 500 controls. MS was associated with a higher frequency of childlessness (22% vs 13%) and less patients were in a stable relationship (83% vs 89%). There was no difference in the reported rates of infertility and miscarriages, while elective abortions were more frequent in patients (20% vs 12%). MS did not significantly affect the frequency of CD or of breast-feeding. MS-related reasons for childlessness, reported by 16% of childless patients, included: disability/fear of future disability, fear of genetically transmitting MS, fear of not starting/discontinuing treatments, discouragement by physician. CONCLUSION Definitive childlessness is more frequent in women with MS compared to controls. A portion of voluntary childlessness may be avoided through correct/tailored information to patients
Response to Reviewers:	Article title: "Definitive childlessness in women with multiple sclerosis: a multicenter study" Submission NEUS-D-16-01064 Dear Professor, I am submitting the revision of the above-said manuscript, after having carefully taken into account all the comments provided by the Reviewers, whom I would like thank for their suggestions. In faith, Diana Ferraro Reviewer #1 1)“There are a few study limitations that are acknowledged by the Authors in the Discussion. Among these, I would add the lack of information on the patients' socioeconomic status that could influence pregnancy decisions.” We have added the above-said limitation in the corresponding paragraph on the limits of the study: “(…) Other limits are the missing data (tables report total number of respondents for each item), due to incomplete questionnaires, and the lack of information on patients' socioeconomic status, which could have influenced family-planning decisions.” 2)“I would also suggest to report and briefly discuss a comparison about breastfeeding figures in MS reported in this sample and in other Italian and international studies published in the recent literature.” In the present study, the rate of breast-feeding was 77% in MS patients and 81% in controls. With regard to the control population, recent data, collected in Italy pertaining to the year 2013, showed that 85.5% of women chose to breast-feed, with an increase in the percentage compared to a previous assessment carried out in 2005, which yielded the exact same figure as that of our control population (81.1%). The duration of breast-feeding has also increased in recent years with a mean duration of 8.3 months in 2013 and 7.3 months in 2005, which is precisely the same value obtained in our control group. This information was provided by the Italian National Institute for statistics (ISTAT). (See: http://www.istat.it/it/files/2014/12/gravidanza.pdf?title=Gravidanza%2C+parto+e+allattamento+al+seno+-+09%2Fdic%2F2014+-+Testo+integrale.pdf) With regard to breast-feeding figures in MS, a systematic review and meta-analysis of studies carried out in different countries reported a breast-feeding rate of 56%, which

was, however, not compared to national expected breastfeeding rates (Finkelsztejn, 2011). In a recent study on 201 German women (Hellwig et al. 2016), 19.4% did not breast-feed at all. This is a slightly lower rate compared to ours (23%), although it has to be kept in mind that our study was carried out on women at the end of the fertile period, on pregnancies which had occurred during previous years and, as highlighted above, there has been an increase in the rate and duration of breast-feeding in Italy in recent years.
Accordingly, the “Breast-feeding“ paragraph in the discussion has been modified as follows:

“There was no significant difference in the proportion of patients and controls deciding to breast-feed. In the present study, the rate of breast-feeding was 77% in MS patients and 81% in controls, which is in line with national data on the rate of breast-feeding (81.1% in 2005, with an increase in recent years: 85.5% in 2013) [27]. With regard to breast-feeding figures in MS, a systematic review and meta-analysis of studies carried out in different countries reported a breast-feeding rate of 56%, which was, however, not compared to national expected breastfeeding rates [9]. In a recent study on 201 German women [23], 19.4% did not breast-feed at all. This is a slightly lower rate compared to ours (23%), although, aside from possible cultural differences, it has to be kept in mind that our study was carried out on women at the end of their fertile period, on pregnancies which had occurred during previous years and, as mentioned above, there has been an increase in the rate of breast-feeding in Italy in recent years. Breast-feeding duration was slightly lower in patients, compared to controls, with no differences, however, between births occurring before or after the diagnosis of MS. The duration of breast-feeding has also increased in recent years in Italy, with a mean duration of 7.3 months in 2005, which is in agreement with data of our control group, and 8.3 months in 2013 [27].”

Reviewer #2

1)“I only suggest to specify whether inclusion/exclusion criteria were used to select controls, and to specify that controls were representative of the general population (as recruited in a Breast Cancer Screening Center it could generate the suspicion of a selected population.”

We enrolled all consecutive subjects at the Breast Cancer Screening Center and did not apply any inclusion/exclusion criteria to select controls.
It is true that, albeit a very high coverage of the screening programme, which is 88% in Emilia-Romagna, Italy (data pertaining the 2010-2015 period, which is even higher than the data originally reported in our manuscript of 86% pertaining to the years 2010-2013) (http://www.osservatorionazionalescreening.it/content/lo-screening-della-mammella-visto-da-passi), subjects may not be fully representative of the general population since, historically, women with lower levels of education and occupation are less likely to undergo cancer screening (Damiani, 2012). However, since there is a negative association of fertility with economic and social development and since highly educated women tend to postpone childbearing (Balbo, 2013), this means that in the present study we may actually have underestimated the differences in the proportion of childless women with MS compared to controls. The following paragraph has been added to the “study Population” paragraph of the discussion:

“We only included women who had reached the end of their reproductive period (>43 years) and, as controls, we chose women participating in the screening programme for breast cancer. Albeit a very high coverage of the screening programme in Emilia-Romagna, Italy, which is equal to 88% (2010-2015 period) [11], subjects may not be fully representative of the general population since, historically, women with lower levels of education and occupation are less likely to undergo cancer screening [12]. However, since there is a negative association of fecundity with economic and social development and since highly educated women tend to postpone childbearing [13], as a consequence, in the present study we may actually have underestimated the differences in the proportion of childless women with MS compared to controls.

Furthermore, we have added the following article, published in Neurological Sciences,

	which is relevant to our article, to the reference list: 1. Cavalla P, Rovei V, Masera S, et al. (2006) Fertility in patients with multiple sclerosis: current knowledge and future perspectives. Neurol Sci 27:231–9. doi: 10.1007/s10072-006-0676-x

Definitive childlessness in women with multiple sclerosis: a multicenter study

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ABSTRACT

OBJECTIVES The frequency of definitive childlessness in women with Multiple Sclerosis (MS) may be higher than in the general population. MS may also affect decisions on the delivery procedure and on breast-feeding issues. Aim of the study was to assess: the frequency of childlessness and its possible causes, the proportion of cesarean deliveries (CD), and the frequency of breast-feeding in patients and controls who have reached the end of their reproductive period.

METHODS Female MS patients (>43 years) and controls (>45 years) filled-out a questionnaire.

RESULTS We enrolled 303 patients and 500 controls. MS was associated with a higher frequency of childlessness (22% vs 13%) and less patients were in a stable relationship (83% vs 89%). There was no difference in the reported rates of infertility and miscarriages, while elective abortions were more frequent in patients (20% vs 12%). MS did not significantly affect the frequency of CD or of breast-feeding. MS-related reasons for childlessness, reported by 16% of childless patients, included: disability/fear of future disability, fear of genetically transmitting MS, fear of not starting/discontinuing treatments, discouragement by physician.

CONCLUSION Definitive childlessness is more frequent in women with MS compared to controls. A portion of voluntary childlessness may be avoided through correct/tailored information to patients.

Keywords: breast-feeding, cesarean delivery, childlessness, fertility, Multiple Sclerosis, pregnancy

Introduction

The frequency of childlessness in Multiple Sclerosis (MS) women may be higher than in the general population [1–3], although studies specifically exploring this issue in women who have reached the end of their fertile period, are lacking.

An increased childlessness in women with MS may be due to a reduced propensity to maternity related to various concerns: about disability/future disability, about genetically transmitting the disease, about the effects of pregnancy on the disease and the effects of the disease on the pregnancy outcome [4, 5]. It may also be due to postponement of maternity while on immunomodulatory drugs, sexual dysfunction caused by MS and, in some cases, infertility brought on by immunosuppressant therapy, although the question as to whether MS may be associated with reduced fertility is still being debated [6, 7].

Furthermore, MS may affect decisions on the delivery procedure, although data on a possible increase in the proportion of planned cesarean deliveries (CD) in MS patients is contrasting [2, 8–11], and on the frequency and duration of breast-feeding, since women with MS may choose not to breastfeed so they can resume their preventive therapies after child-birth.

Objective

The primary objective of the present study was to assess whether there is a higher frequency of childlessness in MS women who have reached the end of their reproductive period, compared to the general population, in a multicenter retrospective prevalence study, and to explore its possible causes.

The secondary objective was to determine the proportion of CDs and the frequency and duration of breast-feeding in MS women compared to the general population.

Methods and Materials

Population

Consecutive female MS patients aged >43 years were enrolled at eight MS Centers in Emilia-Romagna, Italy.

Consecutive control subjects (CS), aged >45 years, were enrolled at the Breast Cancer Screening Center of Modena, Italy.

Following informed consent, all subjects were asked to fill-out a self-administered, anonymous questionnaire, exploring pregnancy issues.

The study was approved by the provincial Ethics Committee of Modena (Prot. 889/2013).

Questionnaires

Women with MS were asked to provide general information (year of birth, nationality, year of MS diagnosis, relationship status, concurrent thyroid problems). Nulliparous patients were asked to indicate the reason/s for being childlessness (and to rank their importance) out of the following list: lack of a stable relationship, no desire for children by patient/patient's companion, financial/social concerns, disability, fear of future disability, fear of genetically transmitting the disease, fear of not starting/discontinuing preventive treatments, sexual dysfunction, infertility, discouragement by neurologist, discouragement by general practitioner, other reasons (which were specified). Parous women were asked: year of childbirth/s, mode of delivery, months to conception, whether assisted reproduction techiniques (ART) were used, occurrence and year/s of spontaneous and elective abortion/s. If a CD occurred, they were asked to indicate the reason out of a list which included the following items: planned for obstetrical/gynecological reasons, emergency procedure, personal or physician's concern in relation to MS diagnosis, other reason. If breast-feeding occurred, they were asked the duration and reasons for discontinuation out of the following list: personal reasons/work issues, problems with breast-feeding, desire to resume preventive treatments for MS, clinical/MRI worsening, other. In case they did not breast-feed, they were asked if the decision was due to personal reasons or to reasons related to MS. Other information provided in the questionnaire is shown in table 2. Control subjects' questionnaires were adjusted by eliminating all items relating to MS.

Statistical methods

Comparisons between groups were made using Student's t-test or the chi-square test, as appropriate. Univariable and multivariable logistic regression was used to assess the impact of collected variables on the risk of childlessness. Data was analyzed using STATA 11 (StataCorp, Texas, USA).

Results

Three-hundred and three MS patients and 500 CS were enrolled in the study. Table 1 and 2 summarize the collected variables.

Childlessness

Sixty-seven MS women (22%) were childless, compared to 66 controls (13%) (p=0.001). The fertility rate (number of children born per woman) was 0.43 in women with MS and 1.45 in controls. The lack of a stable relationship was more frequent in the MS cohort (nr=55; 17% vs nr=59; 11%) (p=0.01). The risk of childlessness was increased by the lack of a stable relationship (OR: 5.6; 95% confidence interval (CI95):3.6-8.7; p<0.001) and by MS (OR: 1.9; CI95:1.3-2.7; p=0.001). After correction for relationship status, nationality and thyroid dysfunction, MS diagnosis still determined a two-fold higher odds of childlessness (OR:1.7; CI95:1.2-2.6; p=0.008) at multivariable analysis.

We found similar rates of miscarriage in MS (nr=57; 24%) compared to CS (nr=99; 24%), but a higher rate of elective abortions (EA) (nr=50 involving 47 patients (20%) vs nr=52 involving 49 subjects 12%) (p=0.005). Of these, 10 (20%) occurred after the diagnosis. There were no differences in the proportion of pregnancies achieved by ART (4; 2% vs 4; 1%).

The main reported reasons for childlessness in MS patients were: no stable relationship (nr=23; 34% of childless patients) and no desire to have children (nr=19; 28%), followed by MS-related issues (nr=11; 17%) and infertility (nr=11; 16%). Twenty-five patients provided additional, secondary reasons for childlessness. Among these, more than half (13/25; 52%) were MS-related (Table 3). Most cited reasons related to MS were: fear of future disability (nr=8; 12% of childless patients), fear of genetically transmitting the disease (nr=6; 9%), fear of not starting/discontinuing treatments (nr=4; 6%), discouraged by physician (nr=3; 4%) and current disability (nr=3; 4%).

In CS, the main reported reasons were: no desire to have children (nr=24; 36% of childless subjects), lack of a stable relationship (nr=15; 23%) and infertility (nr=14; 22%) (Table 3).

Mode of delivery and breast-feeding

A total of 334 live births occurred in the MS group, 43 of which, after the MS diagnosis. There were no significant differences in the frequency of CDs between women with MS and controls (56; 26% vs 89; 21%, respectively). There were no differences in the percentage of women who did not breast-feed (55; 27% vs 82; 19%) though, on average, breastfeeding duration was shorter by 1-3 months in women with MS (Table 1).

Discussion

The present study was primarily aimed at determining the proportion and the possible causes of definitive childlessness among women with MS, compared to the general population.

Study population

We only included women who had reached the end of their reproductive period (>43 years) and, as controls, we chose women participating in the screening programme for breast cancer. Albeit a very high coverage of the screening programme in Emilia-Romagna, Italy, which is equal to 88% (2010-2015 period) [12], subjects may not be fully representative of the general population since, historically, women with lower levels of education and occupation are less likely to undergo cancer screening [13]. However, since there is a negative association of fecundity with economic and social development, and since highly educated women tend to postpone childbearing [14], as a consequence, in the present study we may actually have underestimated the differences in the proportion of childless women with MS compared to controls.

Childlessness in the general population

Childlessness is a term encompassing both voluntary (i.e decision not to have children) and involuntary (i.e not being able to meet childbearing desires) childlessness. The proportion of women aged 40-44 that are childless varies considerably across countries and across times and, according to data from OECD (Organisation for Economic Co-operation and Development), in Italy, 15% of women born in 1960 were definitely childless, with an increase to 20% of women born in 1965 [15]. An increasing trend across more recent cohorts was also observed in the present study, both in patients and controls.

Childlessness and its causes in women with MS

To the best of our knowledge, there are no studies specifically addressing the frequency and possible causes of definitive childlessness in women with MS. A Swedish study showed that, at onset of disease, the proportion of childless women was higher compared to controls of the same age [1]. A French study [16] showed that 34/115 (30%) women with MS were childless, but authors enrolled women who were still in child-bearing age. Alwan et al [17] explored reproductive decision-making in women aged 18-45 who had received a diagnosis of MS during the past 15 years. Approximately 30% of women reported MS-related reasons (mainly “symptoms interfering with parenting”), while the most common non-MS-related reason was “completed their family prior to the diagnosis”. Other studies found that parous women had a reduced risk of MS compared to nulliparous women [18] and authors suggested a reverse causality: women with

future MS may have impaired fertility, though data on the association between MS and reduced fertility is still matter of debate [6, 7]. Data from the present study does not suggest impaired fertility in women with MS since, compared to controls, there are no differences between: the proportion of pregnancies achieved through ART, the frequency of infertility as a reported reason for childlessness, the frequency of spontaneous abortions, the ages at first/second/third/pregnancy, and there is even a reported shorter time to conception in women with MS.

The most frequently reported reason for childlessness in MS women is the lack of a stable relationship (34% of childless patients), and there is a significant difference in the proportion of patients without a stable relationship compared to controls. One may hypothesize that difficulty in starting/keeping a stable relationship may be linked to conditions brought on by the disease such as depression, reduced socialization, disability, reduced propensity to maternity and, in general, to the added stress associated with having a chronic, possibly disabling disease. A study analyzing 2717 couples showed that the onset of a chronic illness was followed in >30% of cases by separation, the risk being higher if the woman became ill [19].

Another interesting aspect is the greater number of EA among women with MS compared to controls and the greater proportion of women with MS undergoing EA (20%) compared to controls (12%), which is similar to that of the general population in Emilia-Romagna: 12.2% [20]**.** Reasons for EA were not explored in the present study, although the question arises as to whether MS-related issues could have lead to the decision of not continuing the pregnancy, when MS diagnosis preceded the EA.

Of note is that, in case of MS-related reasons for childlessness (disability/fear of future disability, fear of genetically transmitting the disease, fear of not starting/discontinuing treatments, discouragement by physician), appropriate and tailored information may possibly have lead to a different decision in some cases. In fact, while in the 1950's and 60's, physicians discouraged pregnancy in MS patients [21], subsequent studies have proved that the long-term outcome is not worse in parous women. Doctors should therefore not discourage a pregnancy because of the diagnosis of MS “per se”, but the decision and the timing, in relation to treatments, should be carefully discussed with the treating neurologist. Finally, nowadays, it is important that patients also receive up-dated information on the safety of treatments, when continued until conception, since the knowledge of not having to discontinue all treatments before trying to conceive [22–24] may be reassuring and help in the decision-making process.

Mode of delivery

Women with MS do not seem to have a higher risk of obstetrical/neonatal complications [10, 11, 25], although there are some contrasting reports [2, 8], and they may undergo planned CDs more frequently compared to the general population, [10] especially if they have a higher disability [11]. The diagnosis of MS alone, should not lead to the decision of a CD, which should be considered should there be concern about spasticity, neuromuscular perineal weakness or exhaustion.[4]. Collaborating and exchanging information with the treating gynecologists and obstetricians in a multidisciplinary approach to the patient could help reduce the frequency of unnecessary CDs, which, in our cohort were more frequent than in the general population, (26% vs 21%), though not significantly so. Moreover, there was no difference in the frequency of CDs between before and after the diagnosis of MS, in the proportion of planned or emergency CDs, nor in the age at CDs between the two groups.

Breast-feeding

There is an ongoing debate as to whether breast-feeding may or not protect against post-partum relapses [26–28], though a large study on 423 pregnancies suggests that the most important determinant of the risk of relapses seems to be the relapse rate before and during pregnancy [29].

Women with MS may be advised by the neurologist not to breast-feed in order to resume preventive therapies, or it may be the woman who independently decides not to breast-feed, for fear of disease reactivation. In our sample, 22 patients (out of the 43 who gave birth after MS diagnosis: 49%) reported a post-partum relapse, occurring after a mean interval of 8 months after child-birth and 27 (63%) resumed a preventive treatment after a mean interval of 13 months.

There was no significant difference in the proportion of patients and controls deciding to breast-feed. In the present study, the rate of breast-feeding was 77% in MS patients and 81% in controls, which is in line with national data on the rate of breast-feeding (81.1% in 2005, with an increase in recent years: 85.5% in 2013) [30]. With regard to breast-feeding figures in MS, a systematic review and meta-analysis of studies carried out in different countries reported a breast-feeding rate of 56%, which was, however, not compared to national expected breastfeeding rates [10]. In a recent study on 201 German women [26], 19.4% did not breast-feed at all. This is a slightly lower rate compared to ours (23%), although, aside from possible cultural differences, it has to be kept in mind that our

study was carried out on women at the end of their fertile period, on pregnancies which had occurred during previous years and, as mentioned above, there has been an increase in the rate of breast-feeding in Italy in recent years.

Breast-feeding duration was slightly lower in patients, compared to controls, with no differences, however, between births occurring before or after the diagnosis of MS. The duration of breast-feeding has also increased in recent years in Italy, with a mean duration of 7.3 months in 2005, which is in agreement with data of our control group, and 8.3 months in 2013 [30]. Nine patients (21%) reported to have stopped breast-feeding because of a relapse and only one to resume therapy.

Limits of the study

The main limit of the study is that it relied on patients' memory of events that occurred in the past. Other limits are the missing data (tables report total number of respondents for each item), due to incomplete questionnaires, and the lack of information on patients' socioeconomic status, which could have influenced family-planning decisions. Moreover, the majority of childbirths in the MS group occurred before the MS diagnosis, so data on CDs and breast-feeding in patients after the MS diagnosis is limited.

Conclusions

MS was associated with a higher frequency of definitive childlessness compared to the control group and significantly less women with MS were in a stable relationship. The most frequently reported reasons for childlessness in MS women were: lack of a stable relationship (34%), no desire for pregnancy, (28%), MS-related issues (17%) and infertility (17%). Reduced fertility did not seem to be an issue in women with MS in the present study: there were no differences compared to controls in the proportion of pregnancies achieved through ART, in the percentage of patients and controls reporting infertility as a cause of childlessness, in the time to conception, in the ages at pregnancies, nor in the rates of miscarriage. EAs, however, were more frequent in the MS group. In our sample, MS did not significantly affect the frequency of CDs nor the frequency of breast-feeding.

MS-related reasons for childlessness were: disability/fear of future disability, fear of genetically transmitting the disease, fear of not starting/discontinuing treatments, discouragement by physician.

A part of voluntary childlessness may be avoided by correctly informing patients/physicians on these issues.

It is, therefore, important that all physicians involved in the management of the woman with MS (including neurologists, gynecologists and general practitioners) convey correct, up-dated and tailored information in order to support women in the decision-making process and to avoid childlessness, where possible, in patients with childbearing desire.

Author disclosures

Authors have nothing to disclose.

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Table 1 Characteristics of patients and control subjects

Variable	**MS (nr. 303)**	**CONTROLS (nr. 500)**	**p-value**
Age (years)[a]	52±7	55±9	<0.001
Italian nationality (nr, %)	280 (95)	456 (93)	n.s
In a stable relationship (nr, %)	248 (83)	441 (89)	n.s
Thyroid dysfunction (nr/total, %)	66/295 (22)	96/492 (20)	n.s
At least one child (nr, %)	236 (78)	434 (87)	0.001
Age at first pregnancy in years [a] (nr subjects) Age at 2nd pregnancy in years [a] (nr subjects) Age at 3rd pregnancy in years [a] (nr subjects)	27±6 (220) 30±5 (94) 32±6 (18)	27±6 (420) 30±5 (266) 32±6 (39)	n.s n.s n.s
At least one CD (nr/total, %)	56/217 (26)	89/431 (21)	n.s
Age at 1st CD in years [a] Age at 2nd CD in years [a] Age at 3rd CD in years [a]	32±6 32±5 33±6	30±7 32±5 33±7	n.s n.s n.s
Reason for 1st CD • gynecol/ostetric. (nr/total, %) • emergency (nr/total, %) • other (nr/total, %)	 24/55 (44) 24/55 (44) 7/55(13)	 38/86(44) 47/86(55) 1/86(1)	 n.s n.s
At least one miscarriage (nr/total, %)	57/239 (24)	99/413 (24)	n.s
Age at first miscarriage (years) [a]	29±7	29±7	n.s
At least one elective abortion (nr/total, %)	47/232 (20)	49/412 (12)	0.005
Age at 1st elective abortion (years) [a]	28±7	29±7	n.s
Months before conception • 1st pregnancy [a] • 2nd pregnancy [a] • 3rd pregnancy [a]	 6±10 11±23 13±23	 8±14 10±21 11±14	 0.048 n.s n.s
Births achieved by ART (nr/total, %)	4/225 (2)	4/429 (1)	n.s
Breast-feeding (nr/total, %)	181/236 (77)	352/434 (81)	n.s
Months breast-feeding • 1st pregnancy [a] • 2nd pregnancy [a]	 6±5 5±4	 7±8 8±8	 0.027 0.009

[a] mean +/- standard deviation

Table 2 MS-related issues in patients

Age at diagnosis (years) [a]	39±9
Reason for breast-feeding interruption 1st pregnancy (nr/total, %): • Personal/work issues • Problems with breast-feeding • MS preventive treatment • Relapse • Other	 56/159 (35) 89/159 (56) 1/159 (1) 9/159 (6) 4/159 (3)
Previous treatment with mitoxantrone (nr/total, %):	22/214 (10)
Preventive treatment after child-birth (nr/total, %):	27/135 (20)
Interval between child-birth and start of preventive treatment (months) *	13±11
Post-partum relapses (nr/total, %):	22/102 (22)
Interval between child-birth and relapse (months) [a]	8±7

[a] mean +/- standard deviation

Table 3 Reported reasons for childlessness in MS patients

	(nr/total, %)
Main reason for childlessness in MS patients	
No stable relationship	23/67 (34)
No childbearing desires	19/67 (28)
Infertility	11/67 (16)
Fear of future disability	5/67 (7)
Fear of transmitting MS	3/67 (5)
Discouraged by neurologist	1/67 (2)
Discouraged by general practitioner	1/67 (2)
Financial issues	1/67 (2)
Disability	1/67 (2)
Fear of discontinuing treatment	1/67 (2)
Sexual dysfunction	0/67 (0)
Other	0/67 (0)
Secondary reason for childlessness in MS patients	
No childbearing desires	4/25 (16)
Fear of future disability	3/25 (12)
Fear of transmitting MS	3/25 (12)
Fear of discontinuing treatment	3/25 (12)
No stable relationship	2/25 (8)
Financial issues	2/25 (8)
Disability	2/25 (8)
Infertility	1/25 (4)
Discouraged by neurologist	1/25 (4)
Discouraged by general practitioner	1/25 (4)
Sexual dysfunction	0/25 (0)
Other	3/25 (12)
Main reason for childlessness in controls	
No childbearing desires	23/64 (36)
No stable relationship	15/64 (23)
Infertility	14/64 (22)
Financial issues	3/64 (5)
Sexual dysfunction	1/64 (2)
Other	7/64 (11)