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## **LONG-TERM EFFECTS OF CHILDBIRTH IN MS**

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Multiple Sclerosis, Childbirth, Pregnancy, Long-Term effects, Disease Progression

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## **Abstract**

**Background:** The uncertainty about long-term effects of childbirth faces MS patients with dilemmas.

**Methods:** Based on clinical data of 330 female MS patients, the long-term effects of childbirth were analysed, using a cross-sectional study design. Four groups of patients were distinguished: (1) without children (n= 80), (2) with children born before MS onset (n= 170), (3) with children born after MS onset (n= 61) and (4) with children born before and after MS onset (n= 19). Time to event analysis and Cox proportional hazard regression were performed with time from onset to EDSS 6 and age at EDSS 6 as outcome measure.

**Results:** After a mean disease duration of 18 years, 55 % had reached EDSS 6. Survival curves show a distinct shift in the time to EDSS 6 between patients with no children after MS onset and patients with children after MS onset in favour of the latter. Cox regression analysis correcting for age at onset shows that patients with children only after MS onset had a reduced risk compared to patients without children (HR 0.61; 95%CI 0.37 – 0.99, p=0.049). Also patients who gave birth at any point in time had a reduced risk compared to patients without children (HR 0.66; 95%CI 0.47 – 0.95, p=0.023). A similar pattern was seen for age at EDSS 6 (HR 0.57, p=0.027 and HR 0.68, p=0.038 respectively)

**Conclusion:** Although a bias cannot fully be excluded, these results seem to support a possible favourable long-term effect of childbirth on the course of MS.

## **Introduction**

MS is a chronic inflammatory disease of the central nervous system and the most frequent cause of disability in young adults. Women are affected about twice as often as men and there are indications that this female to male ratio is changing during the last decades with an increased incidence in women.[1] Female sex is associated with a less severe outcome than male sex.[2] These gender differences indicate a higher susceptibility to MS in women on the one hand and the interaction with some beneficial factors on the other hand.

The disease most often occurs in women of child-bearing age. Therefore, patients are often faced with dilemmas surrounding pregnancy. As for the short term effects of pregnancy, the large prospective European pregnancy study clearly showed a reduction of the relapse rate especially in the third trimester with a threefold increase in the first trimester after childbirth.[3-4] No influence on the disability progression was evident during the follow-up period of two years.[4] Whether pregnancy has long-term effects on disability is not yet resolved. In a Swedish cohort, becoming pregnant after MS onset was associated with a subsequent lower risk of conversion to a progressive course compared with not becoming pregnant.[5] In another study using the time to become wheelchair bound as an index of progression, a significant difference in the time to become wheelchair bound was found between patients with pregnancies after onset of MS (18.6 years) and patients who had no pregnancies after onset of MS (12.5 years), even after correction for age at onset.[6] However, most earlier studies agreed upon the absence of a long-term effect of pregnancy.[4,7-9]

We decided to study this issue in a large group of female patients from our centre, including patients without children and patients who had given birth to children, either before, after or both before and after the onset of MS.

## **Methods**

## Subjects

Patients with MS, attending our MS referral centre, are seen at regular time intervals for evaluation of their neurological status and their medical treatment as well as for multidisciplinary care and/or rehabilitation. At the first visit, baseline demographic and clinical data are collected. During follow up, functional assessments and EDSS measurements are repeatedly performed.

From 2005 until 2007 about 360 female MS patients were under regular care in our centre. All patients fulfilled the diagnosis of MS according to the Poser criteria.[10] The medical records of all these patients were scrutinized for data about the onset of the disease, the type of disease onset and course (relapsing/progressive), the date of the last neurological evaluation, the EDSS at that time point and the year of onset of EDSS 6, if applicable. The year of the first manifestation of neurological symptoms suggestive of MS was taken as the year of onset.

Complete data of 330 female MS patients could be obtained. Patients were divided into 4 groups based on the relationship of childbirth to the onset of MS: (1) patients without children, (2) patients with only children born before the onset of MS, (3) patients with only children born after the onset of MS and (4) patients with children born before and after the onset of MS.

## Statistical analyses

The time to reach EDSS 6 from onset of MS was chosen as the major outcome measure. Time to event plot using time from onset of the disease and EDSS 6 as event stratified by childbirth group were constructed by the Kaplan Meier method, with differences in survival analyzed by the log-rank test. From these Kaplan Meier curves median time to event and 95% confidence intervals (CI) were calculated.

Cox proportional-hazards regression was used to estimate hazard ratios for time from onset to EDSS 6 corrected for the age at onset using dummy variables for the 4 groups in such a way that group 1 (patients without children) was the reference group.

In addition, we used Cox proportional-hazards regression for age at EDSS 6 adjusted for the time at onset of disease using the same dummy variables.

To further explore the data we analysed the subgroup of patients with a disease onset below the age of 30 separately and focussed on the actual age at which they reached EDSS 6. This cut-off was chosen since the likelihood and possibility of becoming pregnant after that age is strongly reduced.

Since the onset of clinical MS may be preceded by a long period of subclinical but biologically active disease in the central nervous system, we also compared patients who gave birth at any point in time to those who did not have children with respect to both the time from onset to EDSS 6 and the age at EDSS 6 after correction for age at onset.

Statistical analyses were performed using the SPSS 15.0 software package (SPSS, Chicago, Illinois). A two-tailed P value of <0.05 was considered statistically significant for all analyses.

## **Results**

Clinical and childbirth data from 330 female MS patients are presented in table 1.

The mean disease duration (standard deviation; SD) was 17.7 (10.5) years and a mean EDSS of 5.6 (2.4) was found at last evaluation. A substantial proportion of patients (24%) had no children at all (group 1). The largest group of patients (52%) had children born only before the onset of MS (group 2). A smaller group (18%) had children born only after the onset of MS (group 3). Group 4 (children born before and after the onset of MS) was the smallest (6%). The age at onset of MS varied between the groups from 22.2 (group 3) to 37.8 years (group 2) with substantial

standard deviations. A mean time of 5.8 years elapsed between the onset of MS and the first pregnancy in group 3.

Characteristics of the subgroup of patients with a disease onset below the age of 30 are given in table 2.

In tables 1 and 2 the median time to EDSS 6 is given for those patients who actually reached that score. We also calculated the median time to reach EDSS 6 from the Kaplan Meier curves of each subgroup. This estimated median time was significantly lower in the first 2 groups, respectively 15 years (95%CI 12-18) and 13 years (95%CI 11-15) than in the last 2 groups, respectively 23 years (95%CI 20-26) and 22 years (95%CI 20-24). The difference in Kaplan Meier estimated median time to reach EDSS 6 was thus 7 to 10 years.

Figure 1 shows the Kaplan Meier curves of the 4 groups. There is a significant difference between the 4 groups ( $p < 0.001$ ) caused by differences between groups 1 and 2 on the one hand and groups 3 and 4 on the other hand. The survival curves show a distinct shift in the time to EDSS 6 between patients having had no children after the onset of MS (groups 1 and 2) and patients having had children after the onset of MS (groups 3 and 4) in favour of the latter groups. Cox regression analysis with the time to EDSS 6 as outcome showed that a substantial part of this effect could be explained by differences between the age at onset of the different groups. However, after correction for age at onset, the group having had children only after the onset of MS still had a reduced risk (HR 0.61; 95%CI 0.37 – 0.99,  $p = 0.049$ ) compared to the group without children (table 3).

Cox regression analysis with the age at EDSS 6 as dependent outcome adjusted for the age at onset, revealed a similar result (table 3).

When comparing patients who never had children to the other patients (thus those who had children at any point in time) both time to EDSS 6 and age at EDSS 6 was significantly in favour

of the latter group (table 3). Figure 2 shows the Kaplan Meier curves for age at EDSS 6 in the two groups. The difference in the curves is significant ( $p=0.004$ ).

In an attempt to minimize the possible confounding impact of age at onset in the analysis, a subgroup of patients with a disease onset below the age of 30 was selected. In this group the same phenomenon was observed: patients not having children had the worst prognosis. The Kaplan Meier estimated median age at which EDSS 6 was reached was 37 years (95%CI 32 – 42) in those not having children as opposed to 43 years (95%CI 41 – 45) in those giving birth to children only after disease onset. The difference between the four groups did not reach statistical significance ( $p=0.062$ , log rank test), which may have resulted from a reduced power due to limited number of patients.

## **Discussion**

The present study of 330 women with a mean follow-up of 18 years after disease onset, suggests that patients who deliver one or more children after disease onset may have a more benign disease course as expressed by either the time to reach EDSS 6 from onset of disease or the age at which EDSS 6 is reached compared to those who had no children after disease onset.

Moreover, women who gave birth at any point in time had less disability progression than those who never had children.

The onset of irreversible EDSS 6 as main outcome measure was chosen because of its frequent use and since it is widely accepted as a robust and clinically relevant disability milestone. Also, this disability score is based upon objective ambulation abilities with good inter-examiner consistency.[11]

The majority of published studies using different methods and outcome parameters in a variable number of patients, ranging from 39 to 185 patients, have reported no long term effects of pregnancy on disability.[7-9] In one study in over 500 patients an apparent but insignificant



trend towards a better prognosis for women with pregnancies after MS onset was found and related to a younger age at onset in this group.[12]

Our findings are in line with 2 earlier studies which used the risk of conversion to a progressive course and the time to become wheelchair bound as endpoint.[5,6] However the potential beneficial effect of pregnancy after MS onset has not been taken seriously before, because of the presumed bias towards a more benign course in those patients and the negative results in several studies.

Indeed, a bias towards a more benign disease course is hard to exclude. Especially a younger age at onset is a likely confounding factor.[2,13] The age at onset of MS was lowest in women with children born after the onset of MS (mean age at onset 22.2 years) and the significance level for the reduced risk of reaching EDSS 6 decreased from 0.001 without correction to 0.049 with correction for age at onset. This suggests a partial confounding effect of the age at onset.

On the other hand, the age at onset effect cannot explain the findings in the subgroup of patients with disease onset before the age of 30. The mean age at onset did not differ between women without children and women with children only after the onset of MS but the median time to EDSS 6 was much shorter in women without children than in women with children only after MS onset. Similarly, no age at onset effect explains why group 2, women with children only born before MS, had a median time to EDSS 6 comparable to that of group 1 despite a difference of nearly 10 years in the mean age at onset of MS.

Another explanation for our findings that needs to be considered is that patients with a more aggressive disease, not related to age at onset, may be less inclined to become pregnant and have children. This would imply that pregnancies after the onset of MS are a consequence of a more benign course of MS and not inducing a more beneficial evolution of MS. Based on our data, this possibility cannot be ruled out. Unfortunately detailed data from all patients about their relapse frequency, progression of EDSS and MRI burden of disease is lacking.

Since the age at pregnancy and MS onset overlap and MS may start biologically years before clinical onset, the timing of pregnancy in respect to disease onset may be less critical than what we present. It is conceivable, although speculative, that pregnancy and childbirth may have delayed the onset of clinical disease in group 2 leading to a relatively shorter time to EDSS 6, compared to groups 3 and 4. Our analyses showed that not only differences were found between group 3 and group 1, but also an association of any childbirth with less severe MS.

Several limitations of the present study need to be pointed out. Firstly, the groups of patients having childbirth after the onset of MS are rather small. This is certainly the case for group 4. This complicates the comparison between the 4 groups. Secondly, data collection was focused on dates of live childbirths and not on numbers of pregnancies or abortions, which could result in incomplete information about hormonal impregnation. Thirdly, there may be an ascertainment bias in the selection of patients followed in our MS center. Although the studied MS population is heterogeneous with representation of different grades of impairment, a bias cannot be excluded. Fourthly, detailed longitudinal information on disease severity (relapse frequency, EDSS progression, MRI) is lacking preventing more comprehensive statistical analyses. Fifthly, we did not take into account the timing and duration of immunomodulatory treatment in the different patient groups. This treatment was gradually introduced during the last 10 years of the study and will not apply to the majority of patients and time. However, immunosuppressive treatments were only used in very selective cases and it is unclear whether this treatment has a serious impact on the time to EDSS 6. Finally, the time to EDSS 6 from onset of MS may not be the correct measure to use. Because the disease may be ongoing for several years before the first relapse occurs, a later clinical onset may give the false impression of a reduced time to EDSS 6. It is therefore reassuring that the analyses using the age at which EDSS 6 was reached obtained similar results.

We can only speculate about the underlying mechanism that could explain a more benign disease course associated with childbirth in women with MS. The most obvious candidates in this respect are sex hormones, which are supposed to play a role in immunomodulation. Studies in animals have shown a protective effect of pregnancy on EAE and an enhanced ability to remyelinate white matter lesions.[14,15] An increase in the generation of new oligodendrocytes and the number of myelinated axons within the maternal CNS has been found as a result of prolactin signalling.[15]

Recent findings in humans also point to an immunomodulatory effect of pregnancy.[16]

Treatment of 10 non-pregnant female patients with the pregnancy hormone estriol resulted in immunologic changes and decreased inflammatory MRI activity during the 6-month treatment period.[17] Furthermore, sex hormones appear to modulate tissue damage in MS. A increased brain damage as measured by the T 1 lesion load on MRI was related to lower serum testosterone levels in women and to lower oestradiol concentrations levels in men.[18] All together, these data are in favour of a role of sex hormones in inflammation, damage and repair mechanisms typical of MS. The mechanisms of this effect are not known.

The favourable effect of pregnancy and childbirth in MS could also point to a long term effect related to a change in lifestyle factors including dietary habits, vitamin intake (vitamin D) and increased indoor and outdoor activities. Alternatively, it could be the result of a short term intervention during a critical period of disease activity, delaying progression to a later phase.

Very recently, 20-year follow-up data of patients with CIS have revealed that (subclinical) disease activity during the first 5 years after CIS is associated with long-term outcome. [19]

Pregnancy during the first 5 years after onset of MS could have a more profound effect on disease activity and delay further progression.

The role of pregnancy and childbirth in MS remains an important issue, since MS affects many women of childbearing age. Based on our results and previous work it is unlikely that there is an

unfavourable long-term effect on disability of giving birth to children after disease onset. In contrast our data rather suggest a possible beneficial effect. These findings may contribute to our understanding of the disease process and the potential role of early interventions.

### **Competing interests:**

The authors report no conflicts of interest.

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## FIGURES

*Figure 1: Kaplan Meier survival curves (time from onset MS) of the four patient groups to reach EDSS 6.*

Legend:

Patient groups:

1. no children
2. pregnancies only before onset MS
3. pregnancies only after onset MS
4. pregnancies before and after onset MS

The curves differ significantly ( $p < 0.001$ ; log rank test)

*Figure 2: Kaplan Meier survival curves (age) of patients with and without children to reach EDSS 6.*

Legend:

Solid line: patients without children; dashed line: patients with children.

The curves differ significantly ( $p = 0.004$ ; log rank test)

Table 1: Characteristics of the four patient groups.

	<b>N (%)</b>	<b>Relapse onset</b> <b>n (%)</b>	<b>Age at onset MS</b> <b>mean (SD; min-max)</b>	<b>Age at first child</b> <b>mean (SD; min-max)</b>	<b>Number of children</b> <b>mean (range)</b>	<b>EDSS 6 reached</b> <b>n (%)</b>	<b>Time to EDSS 6</b> <b>median (IQR)</b>
<b>(1) no children</b>	80 (24)	74 (93)	28.2 (9.7; 13-58)	-	-	42 (52)	8.0 (3.75 – 15.0)
<b>(2) children <u>only</u> before onset MS</b>	170 (52)	143 (84)	37.8 (8.6; 21-68)	25.1 (4.4; 16-40)	1.8 (1-4)	100 (59)	10.0 (6.0 – 14.0)
<b>(3) children <u>only</u> after onset MS</b>	61 (18)	60 (98)	22.2 (4.4; 9-34)	28.0 (4.8; 19-43)	1.6 (1-4)	31 (51)	21.0 (14.0 – 27.0)
<b>(4) children before and after onset MS</b>	19 (6)	18 (95)	28.2 (3.5; 22-35)	25.3 (4.0; 19-31)	2.8 (2-5)	7 (37)	21 (12.0 – 28.0)



Table 2: Characteristics of the subgroup of patients with disease onset before the age of 30.

	<b>N (%)</b>	<b>Relapse onset</b> <b>n (%)</b>	<b>Age at onset MS</b> <b>mean (SD; min-max)</b>	<b>Age at first child</b> <b>mean (SD; min-max)</b>	<b>Number of children</b> <b>mean (range)</b>	<b>EDSS 6 reached</b> <b>n (%)</b>	<b>Time to EDSS 6</b> <b>median (IQR)</b>
<b>(1) no children</b>	48 (32)	47 (98)	22.0 (4.6; 13-29)	-	-	25 (52)	8 (5.0-15.5)
<b>(2) children <u>only</u> before onset MS</b>	32 (21)	29 (91)	26.9 (2.0; 21-29)	22.9 (3.0; 18-29)	1.6 (1-4)	21 (66)	16 (10.5 – 23.0)
<b>(3) children <u>only</u> after onset MS</b>	58 (38)	57 (98)	21.7 (3.9; 9-28)	27.6 (4.8; 19-43)	1.6 (1-4)	30 (52)	21 (14.75 – 27.75)
<b>(4) children before and after onset MS</b>	13 (9)	12 (92)	26.3 (2.1; 22-29)	23.4 (3.3; 19-29)	2.7 (2-5)	6 (46)	21.5 (14.25 – 29.0)

Table 3: Hazard ratios for time from onset MS and age to reach EDSS 6 based on Cox regression analysis after correction for age at onset.

<i>Comparison*</i>	<b>HR</b>	<b>95% CI</b>	<b>p-value</b>
<i>time from onset MS to reach EDSS 6</i>			
Group 3 vs 1	0.61	0.37– 0.99	0.049
Groups (2, 3 & 4) vs 1	0.66	0.47 – 0.95	0.023
<i>age at EDSS 6</i>			
Group 3 vs 1	0.57	0.35 – 0.94	0.027
Groups (2, 3 & 4) vs 1	0.68	0.48 – 0.97	0.032

HR: hazard ratio.

\* patient groups:

1. no children
2. children only before onset MS
3. children only after onset MS
4. children before and after onset MS



