

***Pregnancy and perinatal outcomes among women with multiple sclerosis: A retrospective case-controlled study in South Hungary***  
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**SOURCE**

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## **SUMMARY**

**Background:** Previous studies reported that, the risk of multiple sclerosis on the adverse perinatal and obstetric outcomes are so controversial.

**Objective:** The aim of this study was to investigate the connections between MS and fertility, pregnancy.

**Patients and methods:** The case histories and pregnancy complications in a sample of 65 treatment-naive pregnant women with MS in the period 1998-2012 were compared with an age-matched case-controlled analysis. Comparisons were made between primigravidas and multigravidas subjects.

**Results:** Our results revealed a higher rate of miscarriage (18.46 %) in the first trimester in women with MS, and intrauterine death (7.69 %) in the third trimester, as compared with women without MS ( $p < 0.001$  and  $p = 0.035$ ).

**Conclusions:** These findings suggest that, the risk of miscarriages and intrauterine death may be disease-related not drug-related feature. Further studies are needed to determine to possible associated factors of miscarriages.

**Keywords:** Multiple Sclerosis, treatment naive pregnancy, miscarriage, intrauterine death

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## **BACKGROUND**

Multiple sclerosis (MS) is a chronic progressive immune-mediated demyelinating disease of the central nervous system, that predominantly affects women of reproductive age. Multiple sclerosis has a major impact on career planning, and the family, and it also imposes a social-economic burden. The reported prevalence of MS varies with the geographic region, ranging between 2 and 150 per 100 000 women [1]. The reported prevalence of MS in Hungary is 62/100.000 [2]. The appearance of the disorder is determined by a combination of genetic and exogenous factors [3]. The disease begins with a relapsing course (relapsing-remitting multiple sclerosis), characterized by a wide range of clinical variability, and followed by a progressive phase (secondary progressive multiple sclerosis). The relapses and remissions are not observed in a smaller group of patients, and the symptoms progress from the very beginning (primary progressive form) [4]. It has been widely accepted that, the immunological and hormonal changes that occur during pregnancy, result in a neuroprotective effect with fewer MS relapses [5]. Thus pregnancy does not appear to have a significant effect on the evolution and progression of MS symptoms. However, it seems to be that the medically indicated elective termination of pregnancy among women with MS still occurs in many countries. Recent publications have suggested that the possibility of elevated risk of caesarean section and preterm birth among women with MS [6, 7, 8], but these results not supported by other

studies [9,10]. Previous studies determined a higher risk of miscarriages among these women. These findings were not clearly defined because in some reported studies, elective termination of pregnancy may have been considered by the women and their neurologist and obstetrics and gynaecologist, because of disease progression and the potentially complications of DMD drugs [11,12]. Prevalence of adverse pregnancy outcomes were not establish as being DMD drug-related or MS-related. Although the incidence of MS in Hungary is rather high, the adverse outcome of pregnancy and newborn has not been evaluated to date.

## **OBJECTIVE**

We have reviewed the incidence of obstetric complications in women with MS, and compared them to age matched pregnant women without MS.

The aims of our study was to analyse the incidence of obstetrical and neonatal complications among women with MS and their off springs relative to a neurologically healthy population

## **PATIENTS AND METHODS**

All pregnant patients with relapsing-remitting MS who required obstetrical care at the Department of Obstetrics and Gynaecology in Szeged and were treated in the Department of Neurology in Szeged, were enrolled in our study between 1 January 1998 and 31 December 2012. Their clinical admission charts and documentation were reviewed and analysed retrospectively. The study was approved by the Regional Ethics Committee of the University of Szeged (Approval no.: 194/2010). The research was conducted in full accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki [13,14].

The pregnancies of 65 treatment-naive women with MS diagnosed according to the McDonald criteria as modified by Polman [15, 16] in this period were investigated.

### *Study design*

Pregnancy and neonatal complications (miscarriage, intrauterine death, prematurity, post-term birth, macrosomia, and small for gestational age,) were defined according to the WHO criteria (1960). The control group, selected by simple random sampling, consisted of 65 age-matched pregnant women with no

diagnosis of MS or any other neuro-immunological disorder. The case group was divided into subgroups exposed or not exposed to disease-modifying therapy, into primigravidas or multigravidas subgroups and the control group was also divided to primigravidas and multigravidas subgroups.

The following outcomes were assessed:

- (1) The delivery mode and pregnancy complications.
- (2) The prevalence of malformations and neonatal complications.

#### *Study procedure*

The different groups and subgroups were compared with regard to disorders and obstetrical outcome (vaginal delivery, caesarean section, miscarriage, and intrauterine death) and neonatal outcomes (birth weight, and congenital malformations).

#### *Statistical analysis*

Evaluated parameters were processed by means of SPSS (Statistical Package for Social Sciences) 20.0 with the independent sample t-test for continuous variables and the chi square ( $\chi^2$ ) test for the comparison of proportions. A case-control analysis was used to calculate the odds ratio (OR) and related coverage probabilities for 95% Confidence Intervals (CIs). Fisher's exact test was

performed when an expected variable value was  $<5$ . Results were considered significant with a  $p < 0.05$ .

## RESULTS

In this fourteen years period 102 pregnancies of women with MS observed in our tertiary care centre. From this cohort 65 women were treatment- naive for the disease-modifying treatment.

The maternal and neonatal characteristics and the co-morbidity data in the MS and non-MS groups are presented in **Tables 1- 2**.

**1. General Demographics:** The average age of the primigravidas and multigravidas patients at the diagnosis of MS was  $26.37 \pm 6.34$  years and  $27.72 \pm 3.9$  years, respectively, and the average age at first pregnancy was  $29.65 \pm 4.49$  years and  $25.1 \pm 4.46$  years ( $p > 0.05$ ). The mean EDSS score was non-significantly higher in the primigravidas women with MS than in the multigravidas women ( $1.36 \pm 1.2$  vs.  $1.48 \pm 4.4$ ,  $p > 0.05$ ). The number of married women was significantly lower in the normal population than in the MS population (72.3 % vs. 34.3 %,  $p < 0.001$ ), while a similar number of the MS mothers living in town and in rural areas (46.15% vs. 53.85 %,  $p > 0.05$ ). There was no significant difference between the two groups from the aspects of the education level or the employment status.

**2. Hospitalizations:** Depressive disorders were more prevalent among the women with MS (18.46%) than among the healthy women. ( $p < 0.001$ ) (See in Table 2). The two groups did not differ statistically as concerns other examined parameters. Hospitalization for more than 5 days occurred in 33.85% of the women with MS and in none of the control women ( $p = 0.004$ ), but these significant differences not observed between the primigravidas and the multigravidas (See Table 3 and Table 4.). This finding is related to the MS and the MS-related psychiatric disorders.

**3. Pregnancy Outcome:** Twenty-five (38.46%) women had a pregnancy prior to being diagnosed with MS. The prevalence of vaginal delivery was significantly lower ( $p = 0.042$ ) in the women before their MS was diagnosed. Miscarriages and intrauterine deaths were significantly more frequent in the MS group than the control non-SM group:  $p < 0.001$  and  $p = 0.035$ , respectively. (Table.3) Twelve women had miscarriages (in the period 6-13 gestational weeks) in the case group, and there were 8 cases of intrauterine death in the MS group. Miscarriages were also significantly more frequent among the multigravidas MS women than in the primigravidas MS group ( $p = 0.003$ ), whereas intrauterine death was not significantly more frequent in the primigravidas MS group. ( $p = 0.084$ ) (Table 4). Macrosomia was similar in the both subgroup. The average birth weight was  $2759 \pm 1135$ g in the primigravidas

subgroup, and  $3221.5 \pm 620.8$ g in the multigravidas, subgroup, and these differences were not significant.

**4. Other perinatal outcomes:** Other perinatal outcomes (prematurity, post-term birth, macrosomia) did not differ from those in the control group. The maternal and neonatal data for the primigravidas and multigravidas MS groups are detailed in Table 4.

There were 3 spontaneous twin pregnancies in the MS group (4.62%), which is higher than the multiple pregnancy rates in the general population (1:85). There were no multiple pregnancies in the control group. Data relating to the mode of delivery and the neonatal parameters in the MS and non-MS groups are presented in Table 3.

Other examined variables (average birth weight, prematurity, small for gestational age, vaginal delivery, and congenital malformations) were not statistically significantly different to matched-control group. The prematurity (<37 weeks; < 2500 g), post-term birth (>40 weeks), macrosomia (>4500 g) and congenital malformation statistics were similar in the two groups. There were no congenital anomalies in case and in the control group. There was no difference in the rate of caesarean section between primigravidas and multigravidas women with MS. The average foetal weight and rates of prematurity and congenital malformations were similar in the two groups. Only one newborn was admitted to a neonatal intensive care unit (NICU) because of prematurity.

**5. Elective Termination of Pregnancy:** For personal reasons 27 women decided on elective termination of their pregnancy. Only in one case was a medically indicated termination of pregnancy performed because of the progression of the MS symptoms. There was no case of extrauterine pregnancies.

**6. Assisted Reproductive Use:** There were 2 cases of secondary infertility in each of the primigravidas and multigravidas MS subgroups, who were treated with artificial reproductive techniques (ART). There were no significant differences in assisted reproductive techniques (ARTs) in the group primigravidas relative to the multigravidas group.

## **DISCUSSION**

The fact that the numbers who were hospitalized for more than 5 days differed significantly in the MS group and the control group could be explained, by the greater frequency of depressive disorders in the MS group [21].

As concerns essential hypertension and hyperthyroidism, no significant correlation was observed between the compared groups.

Different authors have reported higher rates of early pregnancy loss in MS, with a mean miscarriage rate of 23.8% (range 24.9-31.8%) [17]. Nelson et al. concluded that these adverse outcomes possibly depend on the circulation of maternal antibodies in these mothers during pregnancy [18]. However the limitation of that study was the lack of a healthy control group. To avoid bias we used a matched and neurologically healthy control group, against whom we analysed the pregnant MS population.

We concur that there is a higher rate of miscarriage (18.46 %) in the first trimester in women with MS, and intrauterine death (7.69 %) in the third trimester, as compared with women without MS ( $p < 0.001$  and  $p = 0.035$ ).

It is widely accepted that multigravidas women had a higher chance for foetal losses. We found that the rate of miscarriage among the multigravidas group was significantly higher to those in the primigravidas group. ( $p=0.003$ ). These findings suggest that, women with multiple sclerosis had a higher chance for miscarriage and intrauterine death.

The literature review, by Finkelsztejn et al [17] indicated a mean rate of caesarean section of 41.5%, (range 40.5-42.4) among women with MS in different countries. Dahl et al. [6], reported that the rate of caesarean section was higher among MS women than among healthy ones. We found that the rate of caesarean section among the MS women was significantly higher than among the control group. Vaginal delivery among the MS women was similar to those in the control group. Disagreement with these findings, the rate of vaginal delivery differed statistically significantly in the multigravidas women with MS and in the primigravidas women with MS ( $p<0.001$ ). We also found that lower degree of EDSS suggesting that the elective termination of pregnancy because of MS may not be necessary. Our data are in agreement with those reported by Ramagopalan et al. [19], who concluded that MS does not have a negative impact on the neonatal outcome. The average birth weight and the rates of small for gestational age, preterm birth, post-term birth and postpartum complications (e.g. maternal anaemia) in the MS cases were not significantly different from those in the

control healthy group. However, other authors have demonstrated higher rates of low birth weight and prematurity [6, 7].

The meta-analysis by Finkelsztejn et al indicated increased level of congenital malformations and neonatal death (range 0.37% - 3.3%) [17]. Our failure to confirm this association may be due to the small numbers in our study. We detected no congenital malformations in our MS subgroup. In our study population, intrauterine death was more frequent (11.6%) than reported in the literature, but the cause of this related to the MS and may be independent of the MS treatment. The prevalence of fertility problems that needed ART treatment among our MS women was not particularly high (3.07 %), which indicates, that the disease did not have a negative impact on fertility, at least in the early stages of MS. All ART-treated women belonged in the relapsing-remitting MS group.

Neurologists and obstetricians should work together from the period of preconception care throughout the pregnancy to the time of delivery and breastfeeding in order to ensure the optimum treatment for MS patients in pregnancy. Adequate disease control during reproductive life is of paramount of importance in these women. A questionnaire-based prospective study of contraceptive practices after delivery and particularly during the breastfeeding period is needed in order to provide counselling to these women.

### ***CONFLICT OF INTEREST***

The authors have no conflicts of interest.

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## Appendix

TABLE 1					
Maternal characteristic in the case and control groups					
	Case group n=65		Control group n=65		p
	n	%	n	%	
<b>Highest educational level</b>					
<b>Uncompleted or completed primary school</b>	3	4.62	6	9.23	NS
<b>Secondary school</b>	48	73.85	52	80	
<b>Tertiary</b>	14	21.54	7	10.77	
<b>Marital Status</b>					
<b>Married</b>	47	72.3	19	34.3	<0.001
<b>Single</b>	9	13.85	31	47.05	
<b>Divorced</b>	7	10.77	14	15.68	
<b>Widow</b>	0	0.	1	2.94	
<b>Employment status</b>					
<b>Employed</b>	45	69.23	40	61.54	NS
<b>Unemployed</b>	20	30.77	25	38.46	

<b>Residence</b>					
<b>Urban</b>	30	46.15	24	36.92	NS
<b>Rural</b>	35	53.85	41	63.07	

N.S.: Not statistically significant

TABLE 2.					
<b>Prevalence of co-morbidity</b>					
<b>Co-morbidity</b>	<b>Cases (n=65)</b>		<b>Controls (n=65)</b>		<b>p</b>
	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>	
<b>Gestational diabetes mellitus</b>					
Yes	3	4.62	11	16.92	0.018*
No	62	95.38	54	83.08	
Total	65	—	65	—	
<b>Essential Hypertension</b>					
Yes	4	6.15	5	7.69	NS
No	61	93.85	60	92.31	
Total	65	—	65	—	
<b>Depressive disorders</b>					
Yes	12	18.46	0	0	<0.001**
No	53	81.54	65	100	
Total	65	—	65	—	
<b>Hyperthyroidism</b>					
Yes	1	1.54	0	0	NS
No	64	98.46	65	100	
Total	65	—	65	—	

N.S.: Not statistically significant

TABLE 3	Comparison of delivery mode and neonatal parameters in the case and control groups				
	Women with MS (n=65)		Women without MS (n=65)		p
	n	%	n	%	
Average birth weight (mean±SD) (g)	3004±904.27		3365±552.75		NS
Prematurity (<37 weeks; <2500 g)	3	4.61	8	12.3	NS
Hospitalization for more than 5 days	22	33.85	8	12.3	0.004*
Small for gestational age	3	4.61	0	0	NS
Vaginal delivery	30	46.15	37	56.92	NS
Caesarean section	12	18.46	23	35.38	0.024*
Congenital malformation	0	0	0	0	NS
Miscarriage	12	18.46	0	0	<0.001**
Post-term birth	2	3.08	0	0	NS
Intrauterine death	5	7.69	0	0	0.035*

N.S.: Not statistically significant

TABLE 4					
Comparison of pregnancy and neonatal complications in primigravidas and multigravidas women with MS					
	Primigravidas (n=40)		Multigravidas (n=25)		p
	n	%	n	%	
Average birth weight (mean±SD) (g)	2759±1135		3221.5±620.8		NS
Prematurity (<37. weeks; <2500 g)	1	2.5	2	8	NS
Miscarriage	3	7.5	9	36	0.003**
Post-term birth	0	0	2	8	NS
Macrosomia (>4500 g)	0	0	1	4	NS
Intrauterine death	5	12.5	0	0	NS
Congenital malformation	0	0	0	0	NS
NICU admission	1	2.5	0	0	NS
Caesarean section	6	15	6	24	NS
Vaginal delivery	11	27,5	20	80	<0.001**
Hospitalization for more than 5 days	15	37,5	7	28	NS

N.S.: Not statistically significant



