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Review Article

Multiple Sclerosis and Reproduction

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Abstract

Up to 1950, epidemiological studies suggested pregnancy as a condition related to an increase in relapse risk and to a worse prognosis of MS. There is now enough evidence that pregnancy does not appear to be harmful overall and may even be beneficial. Relapses are rare during pregnancy and are more frequent in the post-partum period. The outcome of pregnancy for the majority of MS patients is not significantly different from that of the general population. But some precautions may be required in advanced or spinal forms of MS. Disease modifying treatments are unsafe in pregnancy and lactation and should be discontinued prior to pregnancy. Breast feeding might have a beneficial effect.

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ABBREVIATIONS

MS: Multiple Sclerosis; RR: Relapse Rate; DMDS: Disease Modifying Drugs; PRISMS: Pregnancy In Multiple Sclerosis; EDSS: Expanded Disability Status Scale; IFN: Interferon; AFP: Alpha Feto Protein; GA: Glatiramer Acetate

INTRODUCTION

Up to 1950, epidemiological studies suggested pregnancy as a condition related to an increase in relapse risk and to a worse prognosis of MS [1,2]. For many years women with multiple sclerosis were actively discouraged form contemplating pregnancy [3], but reliable information was lacking and most opinion offered ex cathedra [4].

The decision to have a baby is always influenced by many factors. For women with MS, there are additional things to consider and questions that swirl around this decision, such as will I have enough energy to raise a child or will I need help, how will a pregnancy affect my health, will I breastfeed or start back on treatment right after the baby is born?

The aim of this review is to try to answer to the following questions:

A. Will pregnancy affect the disease course?

B. What about treatment in pregnancy

C. What about breast feeding

D. Baby outcome in pregnant MS women

PREGNANCY AND DISEASE COURSE

Effect of pregnancy on the short term course of MS

In 1984 we published our work entitled Activity of multiple sclerosis during pregnancy and puerperium [5].

By that time, a number of putative autoimmune diseases were known to show exacerbations post-partum and remissions in second part of pregnancy, but no work has been done for pregnant MS women. In a cohort of 979 MS patients, we performed a retrospective analysis of 388 pregnant women. We determined in each trimester of pregnancy and post-partum the number of relapses and the corresponding relapse rate (RR-relapses per person per year). 338 women with clinical definite or probable MS had 199 pregnancies: 36 at onset of MS; 163 pregnancies in already affected patients. Eighty-five relapses occurred in association with 199 pregnancies, most (65) in the postpartum period, and a low number of relapses (2) were recorded in the last trimester of pregnancy. Comparing the average exacerbation rate of the study group with that of patients with multiple sclerosis in Israel (RR: 0.28), we found a statistically significant decrease in the third trimester (RR: 0.04) and a high increase in the first three months post-partum (RR: 0.82) (Figure 1). Since no statistical difference between the expected and observed number of relapses was found, we thought that this could indicate that pregnancy itself does not aggravate MS but tends to delay the relapses to the post-partum period.

Other retrospective studies were published later on. In 1988, 101 pregnancies of more than 20 weeks were recorded out of a cohort of 52 MS women interviewed by questionnaire. The study showed a significant decrease in relapses in the first and second trimesters, but no increased risk of relapse during the pregnancy period ((9 months of pregnancy and 6 months post partum) [6].

From a population of 351 women affected by clinically definite MS, 70 reported pregnancies during their relapsing–remitting phase (total of 98 pregnancies) [1]. The study confirmed that in MS the relapse rate decreases throughout pregnancy and increases during puerperium (although this last factor was not proven statistically significant).

In 1990 a small prospective study of 8 pregnant women with MS was published. 6 of them had relapses after delivery [7].

In 1998 the first large, prospective study of the natural history of multiple sclerosis in pregnant women (the PRISMS study) analyzed the pregnancy and postpartum course of 254 MS women from 12 European countries. 269 pregnancies were recorded. (8). As compared with the pre-pregnancy year RR (0.7±0.9), the study found a substantially lower RR during the last trimester (0.2±1.0), and a statistically increased RR (1.2±2.0) during the first three months post partum. Thereafter the RR returned to the pre-pregnancy rate. These results confirmed our previous results (Figure 2), notwithstanding the fact that the RR in our cohort was lower than the European one. At 2 years follow up the PRISMS study also showed that the overall rate of progression of disability did not change during the study period [9].

Effect of pregnancy on long term MS course

125 patients with a remittent onset of MS were prospectively followed for a mean 10 years. The overall relapse rate of the pregnancy group (33 women with 49 pregnancies) was lower than that of a control group without pregnancies after MS onset, but similar to that of patients who had children after MS onset, but no pregnancy during follow up. Pregnancy itself did not lead to increased disability [10].

In a retrospective study the medical records of 178 women with multiple sclerosis were reviewed. No differences in the long-term disability of women with no pregnancies, one pregnancy, or two or more pregnancies were found [11].

The association of the number of births and secondary progression was studied in a hospital-based cohort of 277Dutch women with MS. (median disease duration 17 years); 17% of the women had two or more children. Parity did not influence the risk of secondary progression [12].

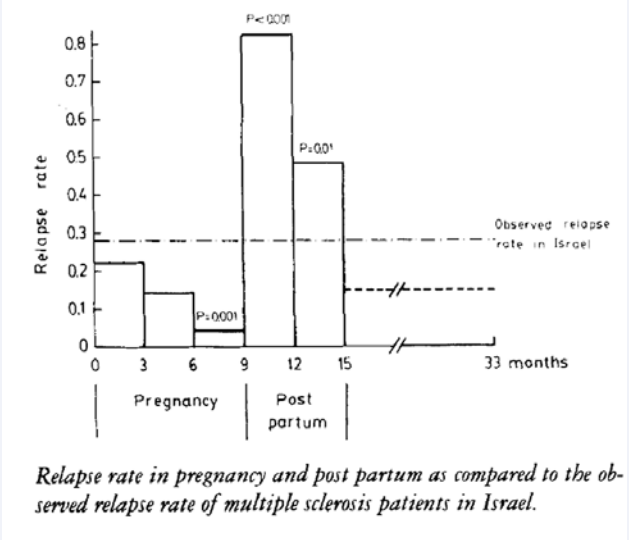

Figure 1 The Israeli cohort.

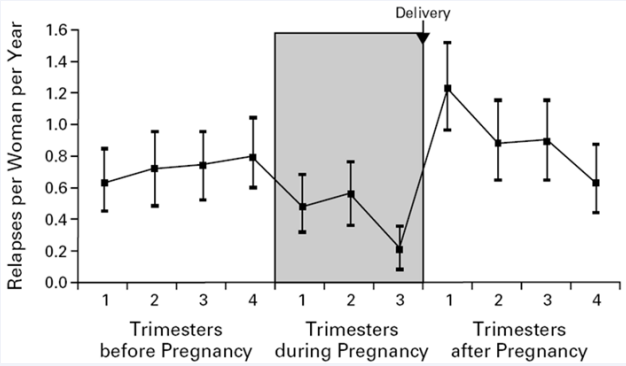

Figure 2 Rate of Relapse per Woman per Year for Each Three-Month Period before, during, and after Pregnancy in 227 Pregnancies Resulting in a Live Birth among Women with Multiple Sclerosis. The values shown are means and 95 percent confidence intervals.

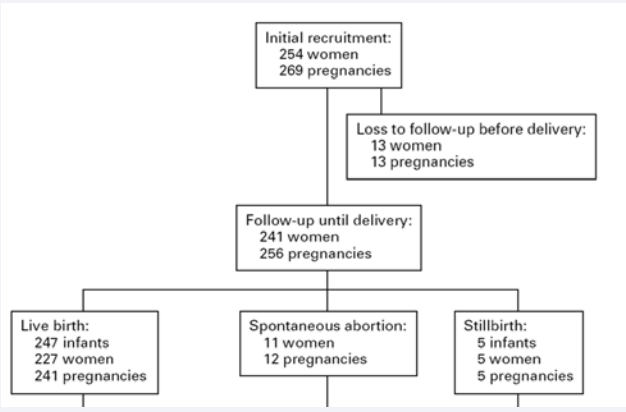

Figure 3 The PRISMS study. Outcomes of Pregnancy and Follow-up in Women with Multiple Sclerosis Who Were Recruited into the Study.

Pregnancy might have a beneficial effect on MS

A cohort of 39 women with definite MS was followed for 5 years. 7 were childless, 10 had onset of MS at least 6 months after last childbirth, and 12 had onset of MS before or in connection with childbirth. At follow up the disability score has deteriorated more for childless women ($p = 0.03$) and women with onset of MS before or in connection with childbirth ($p = 0.005$). The authors conclude that it is unlikely that pregnancy and childbirth have an influence on the long-term prognosis for MS [13].

A study of 200 female Swedish patients with multiple sclerosis investigated whether pregnancy after the onset of disease influences long term disability. Patients who had at least one pregnancy after onset were wheelchair dependent after 18.6 years, versus 12.5 years for the other women ($P < 0.0001$). This difference remained statistically significant after correction for age at onset of disease [14].

In a Belgian MS referral center 330 women were followed up to 18 years after disease onset. Women without children reached a score of 6 at EDSS after 8 years, patients with children only before onset of MS reached EDSS 6 after 10 years and patients who had children before and after onset or only after

onset reached EDSS 6 after 21 years. This study suggests that MS patients who gave birth at any point in time had less disability progression than those who never had children [15].

The underlying mechanisms for spontaneous remission in pregnancy and postpartum exacerbations are not clear

Mechanisms of T cell autoimmunity have been evoked (8). Others suggest a potential role for CD56 bright regulatory NK cells in the control of autoimmune inflammation during pregnancy in MS [16] or the role of the immune-tolerogenic molecule HLA-G in modulating disease activity and pregnancy-related changes [17]. A decline in circulating CD4(+)IFN-gamma-producing cells could lead to postpartum MS relapses. Therefore lactational amenorrhea induced by exclusive breastfeeding may be able to interrupt this process [18]. Sex hormones have been incriminated, since they could have effects on inflammation, damage or repair [19].

We once thought of the possible effect of alpha feto protein AFP, a substance that can inhibit galactocerebroside antibody mediated lysis of oligodendrocytes in vitro. AFP increases in each normal pregnancy and reaches a peak around week 32. However the role of AFP as a potential protective effect on MS relapses was not confirmed [20].

TREATMENT IN PREGNANCY

Most of the disease modulating drugs (DMD) used in the preventive treatment of MS are considered unsafe in pregnancy (pregnancy categories C or D) [21]. Lactation risk for infants cannot be ruled out. Teriflunomide is contraindicated in pregnancy and there is a great concern with cyclophosphamide. (Table 1). While there are no human studies about the pregnancy risk in MS patients treated with DMD, there are some reports in women who became pregnant while been on DMDs.

Exposure to interferon

In 1022 cases: exposed to SC interferon beta-1a during pregnancy, 425 documented outcome for prospective data. Most pregnancies were exposed for less than 45 days. There were 76% normal live births, 11.5% spontaneous abortions. 9.2% of the patients chose elective terminations [22].

Exposure to glatiramer acetate GA

Data were collected on 423 pregnancies in MS patients. 17 women were exposed to GA, 88 were exposed to interferon beta, and 318 were non-exposed pregnancies (suspension of the drug at least 4 weeks prior to conception or never-treated pregnancies). As compared with non-exposure, exposure to GA did not increase the risk of spontaneous abortion, the frequency of premature deliveries was not significantly higher, mean birth weight and lengths were not significantly different [23].

A cohort study of women with highly active relapsing-remitting multiple sclerosis treated with GA throughout pregnancy revealed no serious drug related adverse effects. 14 women became pregnant resulting in 13 live births and 2 spontaneous abortions. Of the 13 live births, 9 were exposed to GA at the time of conception, throughout pregnancy, and following delivery. 11 of the births occurred at term. The mean birth weight of the babies born at term was 3318 g [24].

Exposure to natalizumab

35 women who became pregnant during natalizumab therapy were compared with pregnant MS women non- exposed to DMDs therapies (n=23). Patients were exposed to natalizumab for a short period (median of 22.6 days after last menses, in six patients before the last menstrual period). 28 children were born healthy; there were 5 spontaneous abortions in the first trimester (14%), and one elective abortion. The only malformation recorded was one infant born with minor hexadactyly in week 35 [25].

Exposure to fingolimod

In a very recent report of 66 pregnancies with in utero exposure to fingolimod, there were 28 live births, 9 spontaneous abortions, 24 elective abortions, 4 ongoing pregnancies, and 1 pregnancy with an unknown outcome. Two infants were born with malformations: 1 with congenital unilateral posteromedial bowing of the tibia and 1 with acrania. Elective abortions were performed for 1 case each of tetralogy of Fallot, spontaneous intrauterine death, and failure of fetal development. There were 5 cases of abnormal fetal development in the 66 pregnancies that had in utero exposure to fingolimod. In all 5 cases, fetal exposure to the drug took place in the first trimester of pregnancy [26,27].

Other treatments

Azathioprine is considered relatively safe in pregnancy.

Table 1:

	Pregnancy category	Pregnancy risk	Lactation risk
Interferon beta 1 a	C/D	abortifacient activity in pregnant monkeys and women	Infant risk is minimal
Interferon beta 1 b	C/D	abortifacient activity in pregnant monkeys	Infant risk cannot be ruled out
Glatiramer acetate	B	moderate	Infant risk cannot be ruled out
Natalizumab	C	Risk of abortion	Infant risk cannot be ruled out
Fingolimod	C/D	In animal studies, embryofetal death and teratogenicity, including visceral malformations In humans, cardiac malformations and increased fetal loss	Infant risk cannot be ruled out
Teriflunomide	X	contraindicated craniofacial and skeletal defects	Infant risk cannot be ruled out.
Mitoxantrone	D	potential human teratogen	Infant risk cannot be ruled out
Methyprednisolone	A/C	higher incidence of cleft palate in rats, rabbits, and mice	Infant risk is minimal
Cyclophosphamide	D	positive evidence of human fetal risk	contraindicated
Dimethyl fumarate	C	increased risk of delayed development, small birth size delayed ossification	Infant risk cannot be ruled out

Methotrexate should be avoided (arbortifacient effects and risk of malformations). Oral steroids in pregnancy are generally considered relatively safe. Antispasticity or neuropathic pain medications should be reviewed on an individual basis

BREAST FEEDING IN MS

The PRISMS study showed that neither breast-feeding nor epidural analgesia had an adverse effect on the rate of relapse or on the progression of disability in multiple sclerosis [8].

A possible protective effect of breast feeding was even suggested. Comparing a cohort of 32 MS Californian patients to 29 healthy controls, patients with MS were less willing to breast feed in order resume MS therapies. However women with MS who breastfed exclusively for the first 2 months postpartum were approximately 5 times less likely to relapse in the postpartum year than women who did not breastfeed or began supplemental formula feedings during that time. Women who did not breastfeed or started regular supplemental feedings within the first 2 months postpartum had a significantly higher risk of postpartum relapses during the year following delivery and relapsed earlier [28].

Another opinion is that the reported association between breastfeeding and a lower risk of postpartum relapses may simply reflect different patient behavior, biased by the disease activity. In a sample of 423 pregnancies postpartum relapses were predicted only by relapses before and during pregnancy [29].

BABY OUTCOME

Results of the PRISMS study are shown in Figure C. Infants' mean birth weight was 3.3±0.6 kg. Only 7 infants weighted less than 2.5 kg. One infant had ureteral stenosis. All of the live-born infants were healthy at one year of age except for one who died from sudden infant death syndrome [8].

Women with MS are no more likely to experience delivery complications than women without MS. The mode of delivery should to be decided strictly on obstetrical criteria. Spinal, epidural and general anaesthesia are all safe in MS patients. There is no increased risk of malformations, preterm delivery, low birth weight, or infant deaths [30].

MANAGEMENT OF AN MS PATIENT DURING HER PREGNANCY

MS has no physiological effect on fertility. However sexual dysfunction may impact conception. There is no evidence that contraceptive pill has an adverse effect on MS. Moreover contraception is required during DMD treatment, perhaps even more with the new oral medications which are all small molecules that readily diffuse across the placenta, in contrast to the previously approved drugs that are large recombinant protein molecules [27].

It is recommended to stop the disease modulating treatments DMTs 3 months prior conception for planned pregnancies, and 2 years for teriflunomide [27]. If conception on DMTs does occur, each case has to be discussed, stopping therapy might be considered, and elective abortion discussed. It is recommended not to use DMT during breast-feeding. This consideration must be weighed against the desire to restart DMTs as early as possible in the postpartum period to minimize postpartum relapse risk.

As the pregnancy progresses due to increasing weight: physical therapy, patients may suffer from further reduction in mobility and increased spasticity. Immobile pregnant patients are at risk for thromboembolism. Urinary tract infections are more common in pregnancy on neurogenic bladders [31].

DISCUSSION AND CONCLUSION

MS patients should be reassured that pregnancy does not appear to be harmful overall and may even be beneficial. The outcome of pregnancy for the majority of MS patients is not significantly different from that of the general population. But some precautions may be required in advanced or spinal forms of MS.

REFERENCES

1. Salemi G, Callari G, Gammino M, Battaglieri F, Cammarata E, Cuccia G, et al. The relapse rate of multiple sclerosis changes during pregnancy: a cohort study. Acta Neurol Scand. 2004; 110: 23-26.
2. Douglass LH, Jorgensen CL. Pregnancy and multiple sclerosis. Am J Obstet Gynecol. 1948; 55: 332-336.
3. Argyriou AA, Makris N. Multiple sclerosis and reproductive risks in women. Reprod Sci. 2008; 15: 755-764.
4. McAlpine's Multiple Sclerosis. Alastair Compston, Elsevier Health Sciences, 2005.
5. Korn-Lubetzki I, Kahana E, Cooper G, Abramsky O. Activity of multiple sclerosis during pregnancy and puerperium. Ann Neurol. 1984; 16: 229-231.
6. Frith JA, McLeod JG. Pregnancy and multiple sclerosis. J Neurol Neurosurg Psychiatry. 1988; 51: 495-498.
7. Birk K, Ford C, Smeltzer S, Ryan D, Miller R, Rudick RA. The clinical course of multiple sclerosis during pregnancy and the puerperium. Arch Neurol. 1990; 47: 738-742.
8. Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. N Engl J Med. 1998; 339: 285-291.
9. Vukusic S, Hutchinson M, Hours M, Moreau T, Cortinovis-Tourniaire P, Adeleine P, Confavreux C. Pregnancy and multiple sclerosis (the PRIMS study): clinical predictors of post-partum relapse. Brain. 2004; 127: 1353-1360.
10. Roullet E, Verdier-Taillefer MH, Amarenco P, Gharbi G, Alperovitch A, Marteau R,. Pregnancy and multiple sclerosis: a longitudinal study of 125 remittent patients. J Neurol Neurosurg Psychiatry. 1993; 56: 1062-1065.
11. Thompson DS, Nelson LM, Burns A, Burks JS, Franklin GM. The effects of pregnancy in multiple sclerosis: a retrospective study. Neurology. 1986; 36: 1097-1099.
12. Koch M, Uyttenboogaart M, Heersema D, Steen C, De Keyser J. Parity and secondary progression in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2009; 80: 676-678.
13. Stenager E, Stenager EN, Jensen K. Effect of pregnancy on the prognosis for multiple sclerosis. A 5-year follow up investigation. Acta Neurol Scand. 1994; 90: 305-308.
14. Verdru P, Theys P, D'Hooghe MB, Carton H. Pregnancy and multiple

sclerosis: the influence on long term disability. Clin Neurol Neurosurg. 1994; 96: 38-41.

15. D'hooghe MB, Nagels G, Uitdehaag BM. Long-term effects of childbirth in MS. J Neurol Neurosurg Psychiatry. 2010; 81: 38-41.

16. Airas L, Saraste M, Rinta S, Elovaara I, Huang YH, Wiendl H, et al. Immunoregulatory factors in multiplesclerosis patients during and after pregnancy: relevance of natural killer cells. Clin ExpImmunol. 2008; 151: 235-243

17. Airas L, Nikula T, Huang YH, Lahesmaa R, Wiendl H. Postpartum-activation of multiple sclerosis is associated with down-regulation of tolerogenic HLA-G. J Neuroimmunol. 2007; 187: 205-211.

18. Langer-Gould A, Gupta R, Huang S, Hagan A, Atkuri K, Leimpeter AD, et al. Interferon-gamma-producing T cells, pregnancy, and postpartum relapses of multiple sclerosis. Arch Neurol. 2010; 67: 51-57.

19. Tomassini V1, Pozzilli C. Sex hormones, brain damage and clinical course of Multiple Sclerosis. J Neurol Sci. 2009; 286: 35-39.

20. Lubetzki-Korn I, Hirayama M, Silberberg DH, Schreiber AD, Eccleston PA, Pleasure D, et al. Human alpha-fetoprotein-rich fraction inhibits galactocerebroside antibody-mediated lysis of oligodendrocytes in vitro. Ann Neurol. 1984; 15: 171-180.

21. Truven Health Analytics.

22. Sandberg-Wollheim M1, Alteri E, Moraga MS, Kornmann G. Pregnancy outcomes in multiple sclerosis following subcutaneous interferon beta-1a therapy. Mult Scler. 2011; 17: 423-430.

23. Giannini M, Portaccio E, Ghezzi A, Hakiki B, Pastò L, Razzolini L. Pregnancy and fetal outcomes after Glatiramer Acetate exposure in patients with multiple sclerosis: a prospective observational multicentric study. BMC Neurol. 2012; 12:124

24. Salminen HJ, Leggett H, Boggild M. Glatiramer acetate exposure in pregnancy: preliminary safety and birth outcomes. J Neurol. 2010; 257: 2020-2023.

25. Hellwig K, Haghikia A, Gold R. Pregnancy and natalizumab: results of an observational study in 35 accidental pregnancies during natalizumab treatment. Mult Scler. 2011; 17: 958-963.

26. Karlsson G, Francis G, Koren G, Heining P, Zhang X, Cohen JA, et al. Pregnancy outcomes in the clinical development program of fingolimod in multiple sclerosis. Neurology. 2014; 82: 674-680.

27. Langer-Gould AM. The pill times 2: what every woman with multiple sclerosis should know. Neurology. 2014; 82: 654-655.

28. Langer-Gould A, Huang SM, Gupta R, Leimpeter AD, Greenwood E, Albers KB, et al. Exclusive breastfeeding and the risk of postpartum relapses in women with multiple sclerosis. Arch Neurol. 2009; 66: 958-963.

29. Pastò L, Portaccio E, Ghezzi A, Hakiki B, Giannini M, Razzolini L, Piscolla E. Epidural analgesia and cesarean delivery in multiple sclerosis post-partum relapses: the Italian cohort study. BMC Neurol. 2012; 12: 165.

30. Ferrero S, Pretta S, Ragni N. Multiple sclerosis: management issues during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2004; 115: 3-9.

31. Lee M, O'Brien P. Pregnancy and multiple sclerosis. J Neurol Neurosurg Psychiatry. 2008; 79: 1308-1311.

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