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Impact of multiple sclerosis treatment during pregnancy on child developement

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Original Research Article

The impact of multiple sclerosis treatment during pregnancy on child neurodevelopment

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ABSTRACT

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease with higher incidence in women of childbearing age. Pharmaceutical management during pregnancy of women diagnosed with MS is challenging, since the knowledge of the potential risks for children is limited. The aim of this study was to analyze the effect of disease modifying treatments (DMTs) used during pregnancy on children's neurodevelopment, in a cohort of patients monitored at our center.

Methods

The study sample included children and adolescents aged 2 to 17 years old, whose mothers were on DMTs for MS during their pregnancy, accompanied in our center. The control group, matched for age and gender, was randomly selected in the pediatric emergency department, having a single exclusion criterion, the fact that the mother has MS. The Portuguese version of *Strengths and Difficulties Questionnaire* (SDQ) was used, and the subscales results were compared. Statistical significance was considered when $p<0.05$.

Results

We collected data on 86 pregnancies of 69 women exposed to DMTs, of which 59.3% discontinued it in the first trimester and 16.3% changed to another drug. The study sample included 86 children, with ages and gender distribution not significantly different from the control group. SDQ subscales results were the following (study sample vs control): 86.0% vs. 88.5% for emotional symptoms (p=0.613); 87.2% vs. 87.5% for conduct problems (p=0.953); 91.9% vs. 88.5% for hyperactivity (p=0.454); 96.5% vs 89.6% for peer relationships (p=0.070); and 100% vs 100% for prosocial behavior. No statistically significant association was verified between the SQD subscales of the DMTs-exposed children and the control group, nor when the subgroups of age and gender where considered.

Discussion

Our main results showed no statistically significant differences between the SDQ subscales' score of the study sample and the control group. These findings reassure that DMTs in early pregnancy have no potential impact on child neurodevelopment, considering that most MS patients were treated with first line DMTs and more than half of the patients discontinued the treatment in the first trimester of pregnancy. The higher percentage of abnormal results obtained for emotional symptoms is in line with the prevalence of global mental health issues of current times.

Conclusion

Our study suggests that DMTs exposure during early pregnancy on MS women has no negative effect on children's neurodevelopment and highlights the importance of conducting a multicenter study, for the projection of broader results.

KEYWORDS

Multiple sclerosis, pregnancy, disease modifying treatments, Strengths and Difficulties Questionnaire, children neurodevelopment

1 – INTRODUCTION

MS is a chronic immune-mediated disease in which autoreactive T cells from the peripheral circulation invade the central nervous system (CNS) and induce an inflammatory cascade, leading to demyelination and axonal loss (1,2). The incidence of MS is around threefold higher in women compared to men, being this difference possibly attributable to hormonal differences. The diagnosis of this disease is frequently made at childbearing age (3,4) and, therefore, family planning and treatment strategies prior to and during pregnancy are becoming major concerns. Over recent decades, MS treatment made very significant advances. Several DMTs have been approved by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) (5). These drugs currently represent an early treatment option for women diagnosed with MS, due to their effectiveness in decreasing disease severity and relapses and, consequently, the progression of new CNS lesions, with the consequent disability accumulation. However, regarding pregnancy in women diagnosed with MS, it is important to emphasize that pharmaceutical management is challenging (6). Evidence has mainly been described for pregnant patients taking either glatiramer acetate or interferon beta, while there is still a lack of scientific literature on the highly effective DMTs that have more recently come onto the market (7). Therefore, women are advised to discuss treatment options with their neurologists before planning a family, and, in many cases, it may be recommended, or even required, for a woman to discontinue her treatment with DMTs during pregnancy (8).

Nevertheless, women with MS who plan to become pregnant and interrupt treatment are at greater risk of worsening their disease and compromising motherhood itself. Furthermore, some

women may become pregnant while taking DMTs, and the knowledge of the potential risks to pregnancy and children is still limited. Since no prospective, randomized, double-blind clinical trials have ever been performed for DMTs in pregnancy, the best evidence-based data is only achieved by observational studies, based on real world data (9,10).

Some groups have reported neonatal outcomes in women who received DMTs during pregnancy, namely on obstetric mobility (11), somatometric characteristics, congenital or laboratory abnormalities (2,12–14). The literature on the impact of MS treatments during pregnancy on children's neurodevelopment is scarce and limited. Expanding the investigation of fetal exposure to DMTs, considering children's neurodevelopment, is crucial to discuss the best option for patients with MS who intend to become (or already are) pregnant. Therefore, the aim of this study was to analyze the effect of DMTs during pregnancy on children's neurodevelopment, considering a cohort of women monitored at our center.

2 – METHODS

2.1 – Participants

The study sample included children and adolescents aged 2 to 17 years, whose mothers were being followed up at a tertiary care hospital in Coimbra, Portugal, due to the diagnosis of MS, according to the McDonald criteria (15) and who were on DMTs during their pregnancy. At the time of the manuscript preparation (February 2023), 86 children were eligible for enrollment. Recruitment of the control group, matched for age and gender, was randomly selected in the pediatric emergency department, considering as the only exclusion criterion the fact that the mother had a diagnosis of MS.

2.2 – Definition of exposure

Pregnancy exposed to DMTs was defined as one in which the drug was administered after the last menstrual cycle. The study sample was divided according to mother exposure to DMTs at the beginning and during pregnancy as:

1) 1st line-DMTs (interferon beta, glatiramer acetate and dimethyl fumarate);

2) 2nd line-DMTs (natalizumab and fingolimod);

3) other (intravenous immunoglobulin, azathioprine and corticosteroids).

2.3 – Data collection

Data were collected indirectly by accessing hospital computer medical records (*SClinico*®) and through telephone interviews. We collected data on medication exposure at baseline and during pregnancy, MS disease activity (including relapse rate), and gestational age.

To assess our main outcome, we used the Portuguese version of SDQ, after author's authorization (16). The SDQ is a validated and internationally recognized questionnaire that allows researchers to identify children and adolescents at high risk for mental health problems (17,18). Previous studies have shown that SDQ scores were associated with clinical diagnoses, making this tool a reliable instrument for the screening of emotional and behavioral mental health problems, among children and adolescents (17,19). The SDQ consists of five subscales, each containing five items. The scales measure emotional symptoms, conduct problems, hyperactivity-inattention, peer relationship problems, and prosocial behavior. Respondents indicated on a three-point *Likert-type* scale to which extent a symptom applied to them, using the options "Not true", "Somewhat true", or "Certainly true". Each of the subscales consists of five items, and scale scores range from 0 to 10. A higher score indicates more problems for all subscales, except for the prosocial scale, where higher scores correspond to fewer difficulties in prosocial behavior. For each scale, the score was classified as "normal," "borderline," and

"abnormal". The children included in our study are considered low-risk population, therefore "borderline" results were assumed as "normal". The questionnaires were applied by telephone contact or presential interview and answered by the parents.

2.4 – Statistical analysis

Comparisons of associations for the categorical variables were performed with *chi-square test* (with *Monte Carlo simulation method*, when required) and for the quantitative variables, *Mann-Whitney U-test* was used. The level of statistical significance was set at $p<0.05$ for all analyses. IBM SPSS Statistics® (version 28) was used for statistical analysis.

2.5 – Ethics

This study was approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra, with the participants giving their consent, in the light of Good Clinical Practices, within the scope of the Declaration of Helsinki.

3 – RESULTS

We identified a total of 69 women, resulting in 86 pregnancies eligible for analysis. Baseline characteristics of maternal MS and their pregnancies are summarized in Table 1. The mean women age at the time of MS diagnosis was 26.9 (± 5.2) years (range 12-41) and 97.1% presented a relapsing-remitting course. The mean pregnancy duration was 38.4 (± 1.7) weeks (range 35-41), and most women had no relapses during pregnancy (n=78; 90.7%). From those 8 women that experienced relapses during pregnancy, 4 were treated with corticosteroids, 2 were treated with natalizumab and 2 were untreated.

A total of 86 pregnancies in 69 women with MS exposed to DMTs were analyzed: 40.1% exposed to glatiramer acetate, 38.4% to interferon beta, 12.8% to natalizumab, 11.6% to

intravenous immunoglobulin, 5.8% to dimethyl fumarate, 4.7% to corticosteroids, 2.3% to fingolimod and 1.2% to azathioprine (Table 2). At the beginning of pregnancy, interferon beta (n=33; 38.4%), glatiramer acetate (n=30; 34.9%) and natalizumab (n=10, 11.6%) were the most used treatments (Figure 1). The vast majority (n=51; 59.3%) of DMTs-exposed patients stopped treatment during pregnancy and 14 women (16.3%) changed the DMT, as seen in Figure 2 and in Table 2. The most used treatments during pregnancy were glatiramer acetate (n=16, 18.6%) and intravenous immunoglobulin (n=12; 14.0%). The characteristics of the newborns are summarized in Table 3.

Final study population consisted of 86 children, 16 between 2 and 4 years old, 52 between 5 and 10 years old, and 18 with 11 or more. From those, 46 children were boys and 40 were girls, as described in Table 4. The control group consisted of 96 children and no statistically significant differences were observed between the gender (p=0.940) and mean age (p=0.262) of both groups (Table 5).

The comparative results of the SDQ subscales between study sample and the control group are shown in Table 6. Subscales were not statistically different between both groups, resulting in the following percentages of normal results for the study sample vs. control: 86.0% vs. 88.5% for emotional symptoms (p=0.613); 87.2% vs. 87.5% for conduct problems (p=0.953); 91.9% vs. 88.5% for hyperactivity (p=0.454); 96.5% vs. 89.6% for peer relationships (p=0.070); 100% vs. 100% for prosocial behavior; and 93.0% vs. 92.7% for total difficulties (p=0.934). The higher percentage of normal results (100% for both groups) were obtained for the prosocial behavior. On the opposite, the lower percentage of normal results were obtained for the emotional symptoms (87.2 and 87.5% for study sample and control group, respectively).

There were also no statically significant differences in the SDQ results regarding different subgroups of age, namely 2-4, 5-10 and 11-17 years. Study sample was divided according to mother exposure to DMTs at the beginning and during pregnancy as 1) 1st line-DMTs

(interferon beta, glatiramer acetate and dimethyl fumarate); 2) 2nd line-DMTs (natalizumab and fingolimod); and 3) others (intravenous immunoglobulin, azathioprine and corticosteroids). No statistically significant difference was observed between these DMTs-exposed groups and the control group for SDQ subscales results.

Table 1. Characteristics of mothers with MS and their pregnancies.

Baseline characteristics of MS	**n=69**
Age at MS diagnosis, mean ± SD (min-max), years	26.9 ± 5.2 (12-41)
MS course	
Relapsing-remitting MS, n (%)	67 (97.1)
Secondary progressive MS, n (%)	2 (2.9)
Baseline characteristics of pregnancies	**n=86**
Pregnancy duration, mean ± SD (min-max), weeks	38.4 ± 1.7 (35-41)
Relapses during pregnancy, n (%)	8 (9.3%)
1 relapse, n (%)	6 (7.0%)
2 relapses, n (%)	2 (2.3%)

Table 2. Relationship between the treatment in the beginning and during pregnancy of women with MS.

		Treatment during pregnancy, n						
		Suspended	Intravenous immunoglobulin	Glatiramer acetate	Natalizumab	Azathioprine	Corticosteroids	Total
Treatment in early pregnancy, n	Natalizumab	6	0	2	1	0	1	10
	Interferon	24	7	0	1	0	1	33
	Glatiramer acetate	16	2	11	0	0	1	30
	Dimethyl fumarate	4	0	1	0	0	0	5
	Intravenous immunoglobulin	0	2	0	0	0	0	2
	Fingolimod	1	0	1	0	0	0	2
	Azathioprine	0	0	0	0	1	0	1
	None	0	1	1	0	0	1	3
Total, n		51	12	16	2	1	4	86

Table 3. Characteristics of newborns.

Weight at birth, mean ± SD, g	3076.4 ± 551.7
Length at birth, mean ± SD, cm	47.8 ± 2.8
Cephalic perimeter at birth, mean ± SD, cm	33.6 ± 1.7
Hospitalizations after birth, n (%)	17 (19.8%)

Table 4. Characteristics of the study sample – age and gender.

Group		**2-4 years**	**5-10 years**	**11-17 years**	**Total**
Study sample	**Male**	8	30	9	47
	Female	8	22	9	39
	Total	16	52	18	86
Control	**Male**	9	35	9	53
	Female	12	21	10	43
	Total	21	56	19	96

Table 5. Comparative analysis of age and gender distribution between study sample and controls.

	Study sample	**Control**	***p-value***
Male, n (%)	47 (54.7)	53 (55.2)	0.940
Female, n (%)	39 (45.3)	43 (44.8)	
Age, mean ± SD	8 ± 3	7 ± 3	0.262

Figure 1. Distribution of DMTs exposure in the beginning of pregnancy.

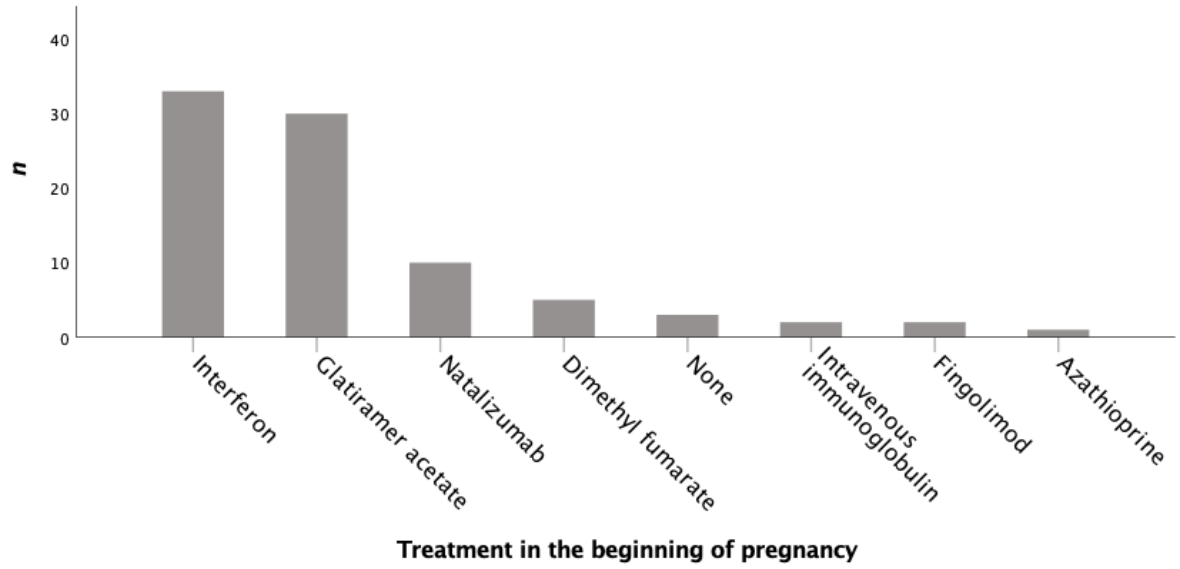

Figure 2. Distribution of DMTs exposure during pregnancy.

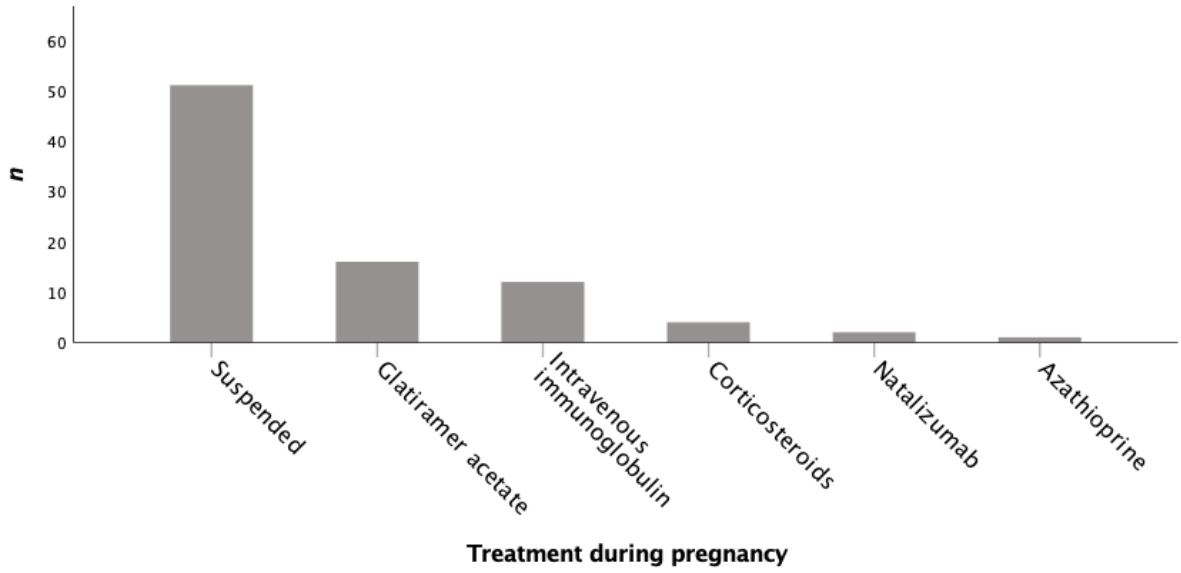

Table 6. Comparative analysis of SDQ subscales of children.

Group	Normal		Abnormal		*p-value*
	n	**%**	***n***	**%**	
	Emotional symptoms				0.613
Study sample	74	86.0	12	14	
Control	85	88.5	11	11.5	
	Conduct problems				0.953
Study sample	75	87.2	11	12.8	
Control	84	87.5	12	12.5	
	Hiperactivity				0.454
Study sample	79	91.9	7	8.1	
Control	85	88.5	11	11.5	
	Peer relationships				0.070
Study sample	83	96.5	3	3.5	
Control	86	89.6	10	10.4	
	Prosocial behavior				-*
Study sample	86	100	0	0.0	
Control	96	100	0	0.0	
	Total difficulties				0.934
Study sample	80	93.0	6	7.0	
Control	89	92.7	7	7.3	

*Prosocial behavior is a constant

4 – DISCUSSION

Potential risk resulting from DMTs exposure during pregnancy is an important issue, since most women develop MS during childbearing age (20). While most current clinical guidelines (21,22) recommend discontinuation of DMTs prior to conception attempts, there is no clear association of DMTs exposure and pregnancy complications (23). The demand for answers among professionals and women with MS of childbearing age is growing, allowing them to better assess the risk and benefits of each DMT, thereby ensuring optimal control of disease activity and no injury for children's outcomes. Previous studies have reported the effect of DMTs exposure during pregnancy on birth outcomes and on disease course, however, to the best of our knowledge, there are no available studies on children long-term neurodevelopment. In this study, we analyzed the relationship between DMTs exposure during pregnancy and children's neurodevelopment.

Our main results showed no statistically significant differences of the SDQ subscales results between the study sample (consisting of children whose mothers were exposed to DMTs in the beginning and/or during pregnancy), and the control group. Most of the children in the study sample were exposed to DMTs in their mothers' wombs during early pregnancy, considering that 59.3% of women with MS had discontinued treatment. The influence of DMTs exposure during pregnancy may be critical to brain development, especially in organogenesis. The three most important stages of neurodevelopmental functioning and development are: 1) the neuron migration until 6 weeks of gestation; 2) synapse formation from the last trimester through the first two years of life; and 3) myelination beginning in the second half of gestation and continuing to adolescence (24). Although our findings reassure DMTs safety and potential no interference in children's neurodevelopment, most MS patients were treated with 1st line-DMTs (40.1% exposed to glatiramer acetate, 38.4% to interferon and 5.8% to dimethyl fumarate) and few were treated with 2nd line drugs (12.8% exposed to natalizumab and 2.3% to fingolimod)

or other drugs (11.6% treated with intravenous immunoglobulin, 4.7% with corticosteroids and 1.2% with azathioprine). Therefore, further studies should be performed with higher representativity of DMTs exposure during pregnancy, so that more reliable conclusions could be obtained. Furthermore, 59.3% of patients suspended DMTs-exposure during pregnancy, but the timing of the respective suspension can be critical for the biological effect on the fetus and our data do not allow a complete answer to this situation.

While the majority of studies report that MS and DMTs exposure do not increase adverse pregnancy outcomes (8,25–27), some studies reveal that mothers with MS are more likely to have infants with low birth weight (21,28–30), low length (31) for the gestational age or prematurely born (28), compared to healthy women. The importance of these findings is due to the association of both birth weight and preterm birth with future health outcomes. Children with lower birth weight have been associated with several cardio-vascular risk factors (32) and are at higher risk of learning difficulties and behavioral problems (33).

Several studies have found that DMTs exposure during pregnancy (mostly only during the first trimester) (34,35) had a significant effect in reducing the relapse rate and disability progression postpartum. High-dose corticosteroid treatment is often used for relapses, which is considered a weak teratogen, with an increased risk for cleft lip or palate and associated with a lower birth weight (26,35). In our study, 8 women had MS relapses during pregnancy and only 4 were treated with corticosteroids, therefore definitive conclusions about the impact of this treatment in children's neurodevelopment cannot be drawn.

The higher percentage of abnormal results (14.0% and 11.5% in the study sample and control group, respectively), although not statically different, were obtained for the subscale of emotional symptoms of SDQ. Our results are in line with the prevalence of global mental health issues, where emotional problems such as anxiety and depression are the two main causes (36)**.** Attention-deficit/hyperactivity disorder is the most common neurodevelopmental disorder in

childhood and adolescence, affecting 2% to 18 % of all school-aged children and adolescents (37,38), which is also in agreement with the values obtained in our study (8.1% and 11.5% of abnormal results in the study sample and control group, respectively). Regarding age association with SDQ subscales results, no statistically significant difference was obtained for the three groups of age.

Potential limitations of the study should also be considered, particularly its retrospective design and the possibility of recall bias in reporting data. The duration and time of DMTs exposure was not considered in this study, due to the limited information being provided in registers/women included in the study. Furthermore, mothers with MS might have a higher predisposition to normalize their answers to the SDQ compared to mothers without MS, by considering that their illness and medication may be responsible for affecting the health of their own children. The evaluation of SDQ subscales is subjective and only the answers given by the parents were considered, therefore a medical evaluation, with more accurate assessment instruments, should be addressed to obtain more reliable conclusions.

5 – CONCLUSION

In our study, we found no statistically significant difference between DMTs exposure in MS during early pregnancy and children's neurodevelopment, as assessed by the SDQ, which provides more reassurance about the safety profile of DMTs in pregnant women. Great variability around the features of pregnancy management in MS patients, the little number of pregnant treated with 2nd-line DMTs, and the lack of a professional medical consultation for children with borderline/abnormal results of the SDQ subscales, highlight the importance of conducting a multicenter study, for the projection of broader results.

6 – REFERENCES

1. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis. Neurology. 2014;83(3):278–86.
2. Burkill S, Vattulainen P, Geissbuehler Y, Espin MS, Popescu C, Suzart-Woischnik K, et al. The association between exposure to interferon-beta during pregnancy and birth measurements in offspring of women with multiple sclerosis. PLoS One. 2019;14(12):1–10.
3. Nicot A. Gender and sex hormones in multiple sclerosis pathology and therapy. Front Biosci (Landmark Ed.) 2009;14(12):4477–515.
4. Harbo HF, Gold R, Tintoré M. Sex and gender issues in multiple sclerosis. Ther Adv Neurol Disord. 2013;6(4):237–48.
5. Thöne J, Thiel S, Gold R, Hellwig K. Treatment of multiple sclerosis during pregnancy – safety considerations. Expert Opin Drug Saf. 2017;16(5):523–34.
6. Añaños-Urrea M, J Modrego P. Interactions between multiple sclerosis and pregnancy. Current landscape of approved treatments. Clin Res Trials. 2020;6(2):1–7.
7. Zanghì A, D'Amico E, Callari G, Chisari CG, Borriello G, Grimaldi LME, et al. Pregnancy and the postpartum period in women with relapsing-remitting multiple sclerosis treated with old and new disease-modifying treatments: a real-world multicenter experience. Front Neurol. 2020;11:105.
8. Hellwig K, Geissbuehler Y, Sabidó M, Popescu C, Adamo A, Klinger J, et al. Pregnancy outcomes in interferon-beta-exposed patients with multiple sclerosis: results from the European Interferon-beta Pregnancy Registry. J Neurol. 2020;267(6):1715–23.
9. Fragoso YD, Boggild M, MacIas-Islas MA, Carra A, Schaerer KD, Aguayo A, et al. The effects of long-term exposure to disease-modifying drugs during pregnancy in multiple sclerosis. Clin Neurol Neurosurg. 2013;115(2):154–9.

10. Schaefer C, Hannemann D, Meister R. Post-marketing surveillance system for drugs in pregnancy—15 years experience of ENTIS. Reprod Toxicol. 2005;20(3):331–43.
11. Cuello JP, Salgado Cámara P, García Domínguez JM, Lozano Ros A, Mas Serrano M, Martínez Ginés ML. Pregnancy exposure to disease-modifying drugs in multiple sclerosis: a prospective study. Med Clin (Barc). 2020;154(6):214–7.
12. Triplett JD, Vijayan S, Rajanayagam S, Tuch P, Kermode AG. Pregnancy outcomes amongst multiple sclerosis females with third trimester natalizumab use. Mult Scler Relat Disord. 2020;40:101961.
13. Andersen JB, Moberg JY, Spelman T, Magyari M. Pregnancy outcomes in men and women treated with teriflunomide. A population-based nationwide Danish register study. Front Immunol. 2018;9:1–7.
14. Friend S, Richman S, Bloomgren G, Cristiano LM, Wenten M. Evaluation of pregnancy outcomes from the Tysabri® (natalizumab) pregnancy exposure registry: A global, observational, follow-up study. BMC Neurol. 2016;16(1):1–9.
15. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162–73.
16. Youthinmind. [updated 2015 september 12; cited 20222 december 12]. Available from: https://www.sdqinfo.org/py/sdqinfo/b3.py?language=Portugueseqz(Portugal).
17. Goodman R. Psychometric properties of the strengths and difficulties questionnaire. J Am Acad Child Adolesc Psychiatry. 2001;40(11):1337–45.
18. Rathgeb C, Schillok H, Voss S, Coenen M, Schulte-Körne G, Merkel C, et al. Emotional situation of children and adolescents during the COVID-19 pandemic in Germany: Results from the COVID-19 Snapshot Monitoring Study (COSMO). Int J Environ Res Public Health. 2022;19(5).

19. Mathai J, Anderson P, Bourne A. The Strengths and Difficulties Questionnaire (SDQ) as a screening measure prior to admission to a Child and Adolescent Mental Health Service (CAMHS). Aust e-Journal Adv Ment Heal. 2002;1(3):235–46.

20. Abramsky O. Pregnancy and multiple sclerosis. Ann Neurol. 1994;36(S1):S38–41.

21. Dahl J, Myhr K-M, Daltveit AK, Hoff JM, Gilhus NE. Pregnancy, delivery, and birth outcome in women with multiple sclerosis. Neurology. 2005;65(12):1961–3.

22. Cree BAC. Update on reproductive safety of current and emerging disease-modifying therapies for multiple sclerosis. Mult Scler. 2013;19(7):835–43.

23. Mahlanza TD, Manieri MC, Klawiter EC, Solomon AJ, Lathi E, Ionete C, et al. Prospective growth and developmental outcomes in infants born to mothers with multiple sclerosis. Mult Scler. 2021;27(1):79–89.

24. Rice D, Barone SJ. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ Health Perspect. 2000;108(Suppl 3):511–33.

25. Burkill S, Vattulainen P, Geissbuehler Y, Sabido Espin M, Popescu C, Suzart-Woischnik K, et al. The association between exposure to interferon-beta during pregnancy and birth measurements in offspring of women with multiple sclerosis. PLoS One. 2019;14(12):e0227120.

26. Thiel S, Langer-Gould A, Rockhoff M, Haghikia A, Queisser-Wahrendorf A, Gold R, et al. Interferon-beta exposure during first trimester is safe in women with multiple sclerosis—A prospective cohort study from the German Multiple Sclerosis and Pregnancy Registry. Mult Scler J. 2016;22(6):801–9.

27. Ebrahimi N, Herbstritt S, Gold R, Amezcua L, Koren G, Hellwig K. Pregnancy and fetal outcomes following natalizumab exposure in pregnancy. A prospective, controlled observational study. Mult Scler J. 2014;21(2):198–205.

28. Chen YH, Lin HL, Lin HC. Does multiple sclerosis increase risk of adverse pregnancy outcomes? A population-based study. Mult Scler. 2009;15(5):606–12.

29. Kelly VM, Nelson LM, Chakravarty EF. Obstetric outcomes in women with multiple sclerosis and epilepsy. Neurology. 2009;73(22):1831–6.

30. Hellwig K, Brune N, Haghikia A, Müller T, Schimrigk S, Schwödiauer V, et al. Reproductive counselling, treatment and course of pregnancy in 73 German MS patients. Acta Neurol Scand. 2008;118(1):24–8.

31. Novo A, Castelo J, de Sousa A, Amorim I, Alves JN, Calejo M, et al. Pregnancy outcomes in Portuguese women with multiple sclerosis: The PREGNIMS study. Mult Scler Relat Disord. 2019;28:172–6.

32. Arnold LW, Hoy WE, Wang Z. Low birth weight and large adult waist circumference increase the risk of cardiovascular disease in remote indigenous Australians-An 18 year cohort study. Int J Cardiol. 2015;186:273–5.

33. Pharoah PO, Stevenson CJ, Cooke RW, Stevenson RC. Prevalence of behaviour disorders in low birthweight infants. Arch Dis Child. 1994;70(4):271–4.

34. Hellwig K, Haghikia A, Rockhoff M, Gold R. Multiple sclerosis and pregnancy: experience from a nationwide database in Germany. Ther Adv Neurol Disord. 2012;5(5):247–53.

35. Villaverde-González R, Candeliere-Merlicco A, Alonso-Frías MA, Aparicio Castro E, Carrillo Alcaraz A, Mallada Frechín J, et al. Discontinuation of disease-modifying treatments in multiple sclerosis to plan a pregnancy: A retrospective registry study. Mult Scler Relat Disord. 2020;46:102518.

36. Valentia S, Turnip SS. Screening for emotional problems: Diagnostic accuracy of the Strength and Difficulties Questionnaire Indonesian version. Asian J Psychiatr. 2022;76:103139.

37. Ayano G, Yohannes K, Abraha M. Epidemiology of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents in Africa: a systematic review and meta-analysis. Ann Gen Psychiatry. 2020;19:21.

38. Rowland AS, Lesesne CA, Abramowitz AJ. The epidemiology of attention-deficit/hyperactivity disorder (ADHD): a public health view. Ment Retard Dev Disabil Res Rev. 2002;8(3):162–70.