The Potential Preventive Effect of Pregnancy and Breastfeeding on Multiple Sclerosis

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Keywords

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Abstract

Background: Multiple sclerosis (MS) is an inflammatory demyelinating chronic neurological disease that affects the central nervous system of young adults and their quality of life. Several studies have investigated the effects of pregnancy and breastfeeding on MS. However, the evidence regarding the influence of pregnancy and breastfeeding on MS is still accumulating. This review aimed to summarize the current evidence regarding the effects of pregnancy and breastfeeding on MS. **Summary:** A systematic electronic literature search of the PubMed and Embase databases was conducted to determine relevant published articles. The eligible studies were summarized and evaluated in tables. **Key Messages:** The majority of the studies indicated that pregnancy appears to lower the rate of MS relapses, particularly in the third trimester. The evidence regarding the effect of breastfeeding on MS remains inconsistent. Despite reports of negative obstetric outcomes in some pregnant women with MS, pregnancies in women with MS should not be categorized as high-risk pregnancies.

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating neurological disease that usually occurs between 20 and 40 years of age [1]. It is a complex disorder with different neurological system dysfunctions that vary in time and place, leading to disability [1]. MS is an immune-mediated disorder that causes an inflammatory reaction and demyelination of the central nervous system neurons. It is initiated by unknown extraneous factors in people with a genetic predisposition, and its underlying mechanisms are not fully understood. The different symptoms depend on the location of the demyelinating lesions [2].

In approximately 80% of the patients, MS may start with a relapsing-remitting pattern (RRMS); in 10–15%, it may be progressive (PPMS). In the natural history of untreated MS, 50% of untreated RRMS patients will gradually convert to secondary progressive MS (SPMS). Early identification of definite MS cases and treatment will reduce the relapses and delay disease progression and disability [3].

MS prevalence is increasing. It affects more women than men with a ratio as high as 3.2:1, particularly in the

reproductive years, which makes pregnancy and labor in women with MS a particular concern [1, 4]. Previously, doctors advised patients with MS to avoid pregnancy because of concerns regarding adverse effects on the disease course [5]. Since the 1950s, pregnancy has been recommended as safe for patients with MS [6]. Investigators have explored the epidemiological, immunological, and therapeutic aspects of the relationship between pregnancy and MS [7–11]. Several analyses, including systematic reviews and a national consensus, have been published, and the majority concluded that pregnancy has a protective effect on MS, and these pregnancies should not be considered as high risk [3, 12–15]. However, the influence of breastfeeding on MS is still debated. This review aimed to examine and discuss the evidence regarding the effects of pregnancy and breastfeeding on MS.

Methods

PubMed and Embase databases were systematically searched for relevant studies published between January 2010 and September 2020 with no language restriction. Randomized clinical trials, nonrandomized clinical trials, prospective and retrospective cohorts, case-control studies, case reports, and case series were included. Animal studies were excluded. The study selection was in 3 stages: in the primary screening stage, an electronic search was conducted using the following terms: “(pregnant* OR gestational OR trimester OR “breastfeeding”) AND (multiple sclerosis) AND (incidence OR prevalence OR prognosis OR complication OR risk OR treatment OR prevent*).” Article titles and abstracts were then screened. The secondary screening stage involved the assessment of the full-text manuscripts. Finally, in the inclusion stage, studies that met our eligibility criteria were extracted. Tables 1 and 2 summarize these studies. The relevant original research studies published from the year 2001 onward were also included.

Review Findings

Effects of Pregnancy on MS

Although the course of MS is highly unpredictable, disease activity in pregnancy is lower than in the prepregnancy period [16–25]. A beneficial effect of pregnancy on disease progression has been found by some researchers, whereas others found that parity was not related to secondary disease progression [16, 26]. The Australian multicenter study of the environment and immune function Ausimmune also showed that parity confers an approximate 50% risk reduction for the first episode of clinical demyelination, with the lowest risk in multiparous women [27].

Relapse Rate

Confavreux and colleagues conducted the first prospective multicenter study addressing the relation of pregnancy with relapse rate. The Pregnancy in Multiple Sclerosis (PRIMS) study recruited 254 pregnant women from 12 European countries [7]. The annualized relapse rate (ARR) of MS decreased from 0.7 to 0.2 relapses per year during the third trimester of pregnancy compared with that in the prepregnancy year. However, postpartum, the ARR increased to 1.2 relapses per year. The clinical predictors have higher ARR in the year before pregnancy, an increased number of relapses during pregnancy, and a higher Expanded Disability Status Scale (EDSS) score at the beginning of pregnancy [28].

One of the largest international studies to evaluate pregnancy's effect on the relapse rate of MS used data from the worldwide MSBase Registry [22]. In 893 pregnancies in 674 women with MS, it showed a drop in relapse rates to minimum 50% lower than that observed in the PRIMS study, with no change in EDSS. The ARR dropped from 0.3 in the preconception period to 0.1 in the third trimester and increased to 0.6 in the early postpartum period [22]. The strong predictive factor for postpartum relapse was preconception ARR. The study also showed that the preconception use of disease-modifying therapies (DMTs) was associated with a 45% reduction in postpartum relapse.

Portaccio et al. [29] correlated disease activity before and during pregnancy with postpartum relapses. Additionally, Bsteh et al. [30] investigated the possible predictors for relapse frequency in pregnancy and after delivery. Disease activity before and during pregnancy and the preconception use of highly active DMTs were essential predictors for relapses in pregnancy and the postpartum period [30]. Early resumption of DMTs reduced the rate of postpartum relapses [29, 30].

Dobson et al. [31] conducted the largest international single-arm meta-analysis of pregnancy-associated MS relapse rates over time. It included all the studies conducted since 1998 covering 7,034 pregnancies in 6,430 women. The ARR decreased from 0.57 in prepregnancy to 0.36, 0.29, and 0.16 during trimesters 1, 2, and 3, respectively, with a postpartum rebound of 0.85, which showed a lower relapse rate at all time points [31].

Pregnancy is a natural disease modifier in MS patients. There could be an upregulation of T helper 2 cells (anti-inflammatory effect) and interleukin-10 cytokines by the placenta during pregnancy, instead of Th 1 (proinflammatory effect). The increase in the postpartum period can also be explained by the modest humoral immunity state

Table 1. A summary of studies on the effect of pregnancy on MS

Reference	Year	Study design	Sample size	Main relevant findings
<i>Relapse rate</i>				
Salemi et al. [16]	2004	Cohort study	70 women	Relapse rate decreased during pregnancy and increased after delivery
De Las Heras et al. [17]	2007	Retrospective multicenter study	88 pregnancies in 74 patients	Relapse rate was lower during pregnancy and increased in the postpartum period Rate of abortions or anomalies did not increase with accidental exposure to immunomodulatory therapy
Saraste et al. [18]	2007	Prospective cohort study	42 women	Disease activity declined at pregnancy and increased after delivery The level of NK cells correlate with disease activity Resuming postpartum treatment early reduce relapses
Hellwig et al. [19]	2008	Retrospective study	88 pregnancies in 73 women	ARR reduced during pregnancy and increased in first 3 months postpartum Infants of MS women had lower weight and height than infants of age-matched controls with single full-term delivery
Fernández et al. [20]	2009	Retrospective multicenter study	141 pregnancies in 81 women	Relapses decreased in the second and third trimesters of pregnancy and increased after delivery High frequency of birth defects was detected among newborns exposed to immunomodulatory therapy in utero
Fragoso et al. [21]	2009	Retrospective multicenter study	49 pregnancies in 47 pregnant women	Low relapse rate was observed during pregnancy There was no significant increase in relapses after delivery Poor gestational outcomes were not associated with the use of different drugs, disability scale, and onset of disease
Hughes et al. [22]	2014	Case-control study	893 pregnancies in 674 females with MS	The ARR (standard error) reduced from 0.3 (0.02) in the prepregnancy period to 0.1 (0.03) in the third trimester and increased to 0.6 (0.06) in the first 3 months postpartum Median EDSS score remained the same in all periods
Fares et al. [23]	2016	Prospective multicenter cohort study	29 women	Compared with the preconception period, relapse rate significantly decreased during pregnancy and in the first year postpartum Increase in relapse rate in the second year postpartum was reported For the third and fourth years postpartum, the ARR mildly decreased but did not change from prepregnancy year
Lai et al. [24]	2018	Prospective cohort study	15 pregnancies in 14 women	The average ARR during pregnancy was lower than before pregnancy; $p = 0.03$ The average score for EDSS increased from 0.7 ± 1.3 at conception to 1.5 ± 1.7 1 year after delivery; $p = 0.04$
Novo et al. [25]	2019	Multicenter retrospective cohort study	97 women and 90 live births	No negative impact of pregnancy on MS relapse rate or children's perinatal health was found
Koch et al. [26]	2009	Retrospective cohort study	277 women	Parity is not associated with disability The number of pregnancies does not affect disability
Ponsonby et al. [27]	2012	Multicenter case-control study	Cases = 282 women Controls = 542 women	Among women, gravidity and parity were associated with a lower risk of the first clinical demyelinating event
Portaccio et al. [29]	2014	Prospective cohort study	350 in 345 women	Higher disease activity before and during pregnancy correlates with the high rate of postpartum relapses and disability accrual Fewer postpartum relapses can be achieved by early restarting of DMTs
Bsteh et al. [30]	2018	Cohort study	387 pregnancies in 239 women	Predictors for relapse and disability progression in pregnancy include relapse activity before conception, high disability score at conception, the preconception use of natalizumab and fingolimod, and long washout period Predictors for postpartum relapse and disability progression include relapse activity before conception and at pregnancy and the use of natalizumab and fingolimod The rate of postpartum relapses will decline with early resumption of DMTs

Table 1 (continued)

Reference	Year	Study design	Sample size	Main relevant findings
<i>Effect of consecutive pregnancies</i>				
Benoit et al. [34]	2016	Prospective cohort study	93 women who had 2 successful pregnancies	Within 3 months of delivery, relapses occur in 31.2% of women after the first pregnancy and 23.7%, after the second pregnancy ($p = 0.3$) Nearly 7.6% of women experienced a relapse after both pregnancies No association was found between the risk of relapse after the second pregnancy and the frequency of relapses in the year before pregnancy or during pregnancy or with the occurrence of a relapse after the first pregnancy
D'Amico et al. [35]	2016	Retrospective cohort study	86 women	No association was found between the number of pregnancies and long-term disability
Altintas et al. [36]	2015	Retrospective clinical study	558 pregnancies in 199 MS patients	An inverse correlation was observed between the number of pregnancies and the rate of conversion from RRMS to SPMS MS group has a lower fertility rate than that in the general population ($p < 0.001$)
D'Hooghe et al. [37]	2012	Retrospective cohort study	973 women	Multiparity is associated with a low risk of progression in RRMS compared with nulliparity Difference in disability was not detected among PPMS or monoparous women compared with nulliparity
Masera et al. [38]	2015	Retrospective cohort study	445 women	Time to disability is longer in the parous group than in the nulliparous group High parity decreased the risk of disability
<i>Long-term progression or conversion</i>				
Keyhanian et al. [39]	2012	Cohort study	102 women	Despite the insignificant increase in ARR 3 months postpartum, a reduction in the ARR 6 years postpartum was observed The mean EDSS was not increased years after follow-up
Ramagopalan et al. [41]	2012	Retrospective cohort study	2,105 women	Pregnancy had no influence on time to disability
Karp et al. [40]	2014	Retrospective cohort study	1,317 women	Pregnancy seems to have no effect on long-term disability
Bsteh et al. [42]	2016	Retrospective cohort study	793 patients with relapsing-remitting MS	No significant differences were identified between the study groups (i.e., the 3-disability outcome groups), with respect to any pregnancy-related data
Zuluaga et al. [43]	2019	Prospective cohort of patients with CIS	501 female participants	Results of univariate analysis (only) showed that pregnancy before CIS was protective for CDMS, but pregnancy after CIS was protective in both analyses (univariate and multivariate)
D'Hooghe et al. [44]	2010	Retrospective cohort study	330 women	Pregnancy decreases long-term disability compared with nulliparity
Jokubaitis et al. [45]	2016	Retrospective cohort study	2,466 women	Lower EDSS scores have been observed among pregnant women compared to nonpregnant women
Lebrun et al. [46]	2012	Prospective longitudinal study	60 women with RIS 53 nonpregnant patients	The pregnant group had a significantly shorter time of conversion to the first neurological event 15.3 months (10–18) than that of the nonpregnant group 35.7 months (8–76) The pregnant group had significantly higher number (mean±SD) of active lesions on a brain MRI scan (3.2 ± 1.7) than that of the control group (1.8 ± 0.6)
<i>Obstetric outcomes and motherhood decisions</i>				
Cuello et al. [47]	2017	Prospective cohort study	MS = 35 women, 40 deliveries Control = 58 women, 60 deliveries	There was no difference in relapse and disability score before, during, and after delivery There was no difference in obstetric outcomes between the study groups

Table 1 (continued)

Reference	Year	Study design	Sample size	Main relevant findings
Dahl et al. [48]	2005	Nationwide historic cohort study	MS group: 649 births Control group: 2.1 million births	Women with MS had a higher rate of having small-for-gestational age newborns and increased need for intervention at delivery
Dahl et al. [49]	2006	Nationwide historical cohort study	MS group: 449 births Control group: 851,060 births	The induction of labor and intervention during delivery were higher among patients with MS Newborns of women with MS had lower length and birthweight
van der Kop et al. [50]	2011	Retrospective cohort study	432 with MS and 2,975 without MS	There were no significant differences between children born to women with MS and those born to non-MS women regarding the mean gestational age or birth weight There was no significant association between MS and assisted vaginal delivery or cesarean section
Chen et al. [51]	2009	Population-based cohort study	174 with MS 1,392 controls	Women with MS had poorer gestational outcomes than those without MS The rate of cesarean deliveries was higher among women with MS
Kelly et al. [52]	2009	Large national database study	10,055 deliveries in women with MS	Increases in the rate of antenatal hospitalization and cesarean sections were detected among MS women
Roux et al. [53]	2015	Cohort study	115 patients	The mean age at the occurrence of spontaneous miscarriages before the onset of MS was comparable with the mean age after MS onset The rate of miscarriage following spontaneous pregnancies was 18.9% MS women have a lower number of children per woman (1.3) compared those in the general population (1.9)
Carvalho et al. [54]	2014	Cohort study	100 women	Motherhood decision was not associated with the type of MS and the frequency of relapses The number of pregnancies differed by the diagnosis of MS (the number of pregnancies was lower than what was planned before the diagnosis of MS)
<i>DMTs and pregnancy</i>				
Weber-Schoendorfer and Schaefer [55]	2009	Prospective observational cohort study	IFN- β group = 69 GA group = 31 MS without exposure = 64 Healthy group = 1,556	Exposure to GA or IFN- β had no specific adverse pregnancy outcome compared with that in other groups in the study
Fragoso et al. [56]	2010	Retrospective and multicenter case series	11 women with MS	GA use throughout pregnancy was not associated with obstetric complications The rate of postpartum relapses was significantly lower than antenatal rates in these cases There were no specific neonatal complications
Giannini et al. [57]	2012	Prospective cohort study	423 pregnancies	There was no significant association between GA exposure and increased risk of spontaneous abortion The frequency of preterm delivery was not significantly associated with exposure to GA There was no difference in mean birth weight and length between the study groups
Lu et al. [58]	2012	Retrospective cohort study	311 women with 418 deliveries	The frequency of assisted vaginal delivery was higher among women exposed to DMTs (IFN- β and GA)
Patti et al. [59]	2008	Retrospective cohort study	38 women	IFN- β exposure early in pregnancy was not related to the adverse outcome of pregnancy and deliveries. A similar finding was observed in women who discontinued IFN- β 1 month before conception

Table 1 (continued)

Reference	Year	Study design	Sample size	Main relevant findings
Amato et al. [60]	2010	Cohort study	396 pregnancies in 388 women	There was no association between IFN- β exposure and the risk of spontaneous abortion Exposure to IFN- β is a predictor of preterm delivery Over a median follow-up of 2.1 years, no fetal or developmental abnormalities were detected
Dung and Panda [61]	2014	Case report	1 woman	Interferon β -1a had been received throughout pregnancy with no relapses or complications Delivered healthy child with normal birth weight and no anomalies
Coyle et al. [63]	2014	Observational study	99 pregnant women	IFN- β -1b exposure was not related to an increase in rates of birth defects and spontaneous abortions Four-month follow-up of the newborn showed no developmental abnormalities
Boskovic et al. [64]	2005	Longitudinal controlled cohort study	64 pregnancies in 46 women	Exposure to beta interferon therapy in the first trimester of pregnancy is correlated with a high rate of miscarriages and low birth weight
Hellwig et al. [65]	2011	Prospective cohort study	Natalizumab = 35 Control = 23	Natalizumab exposure in early pregnancy was not associated with any adverse pregnancy outcomes There was no change in disease activity during pregnancy or after delivery after withdrawn natalizumab
Amato et al. [66]	2015	Prospective cohort study	32 pregnancies	Pregnancy did not prevent disease activation after the discontinuation of natalizumab
Hoevenaren et al. [67]	2011	Case series	2 women	The first case was exacerbated during the antenatal course, but the second case had no relapses while still using natalizumab Delivered healthy newborns and follow-up for 6 weeks showed no abnormalities
De Giglio et al. [68]	2015	Case series	4 women	A sudden increase in disability and MRI lesions was found after the interruption of natalizumab
Friend et al. [69]	2016	A retrospective cohort study	369 patients with MS and 7 patients with Crohn's disease	The risk of pregnancy loss among women exposed to natalizumab is comparable with that in the general population The continuation of natalizumab treatment during pregnancy by 4 patients did not result in any congenital anomalies
Massey et al. [70]	2017	Case report	1 woman	Natalizumab restarted in the second trimester, and the patient eventually recovered physical and cognitive abilities and recovered to baseline The patient delivered a healthy child by elective cesarean section at 40 weeks of gestation
Van Obberghen et al. [71]	2017	Case report	1 woman	Interruption of natalizumab led to early signs of diabetes, elevated liver enzymes, skin reactions, and hypothyroidism The case had a normal delivery
Bayas et al. [72]	2011	Case report	1 woman	Normal prenatal and postnatal development of the newborn was observed after accidental administration of natalizumab in the third trimester
Fagius and Burman [73]	2014	Case report	1 woman	Normal course of pregnancy with normal delivery after continuing natalizumab during pregnancy
Portaccio et al. [74]	2018	Cohort study	92 pregnancies in 83 women	Natalizumab exposure during pregnancy was significantly associated with spontaneous abortion ($p < 0.001$) Exposure to natalizumab and interferon- β (IFN- β) at pregnancy was significantly associated with the lower length and weight of babies ($p < 0.001$)

Table 1 (continued)

Reference	Year	Study design	Sample size	Main relevant findings
Ebrahimi et al. [76]	2015	Prospective, controlled observational study	101 women	There was no significant difference in the rates of major malformations and premature birth between the study groups (natalizumab exposed vs. disease matched vs. healthy control) Compared with that in the healthy group, a significant increase in miscarriage rate and lower birth weights occurred among the MS groups There was no significant difference in the rate of miscarriages and lower birth weights between exposed and disease-matched groups
Schneider et al. [77]	2013	Case series	2 neonates	The use of natalizumab during pregnancy resulted in an uneventful birth A decrease in CXCL12-induced T-cell chemotaxis was detected in both children The chemotaxis rate of unstimulated T lymphocytes was not changed The distribution of the lymphocyte subpopulations was examined in 1 patient only, and it was normal
Haghikia et al. [78]	2014	Case series	12 women and 13 pregnancies	After exposure to natalizumab in the third trimester, natalizumab was detectable in umbilical cord blood in some samples Ten pregnancies had mild to moderate hematologic abnormalities including thrombocytopenia and anemia
Ciron et al. [79]	2016	Case report	1 woman	After exposure to natalizumab throughout pregnancy, the newborn had thrombocytopenia at birth Blood count normalized 10 days after delivery
Guilloton et al. [80]	2017	Case report	1 woman	Natalizumab treatment throughout pregnancy resulted in uneventful pregnancy with regular follow-up A discreet pancytopenia, with leucopenia, thrombocytopenia, and normocytic normochromic anemia, was detected in the neonate blood
Cheraghmakani et al. [83]	2019	Case report	1 child	The use of fingolimod in the first trimester is linked to global developmental retardation, hypotonia, truncal ataxia, and autistic features in a child
Karlsson et al. [84]	2014	Phase II, phase III, and phase IV clinical studies	74 pregnancies in fingolimod	Data regarding the fetal safety of fingolimod are limited Effective contraception during and 2 months after stopping fingolimod is recommended
Sempere et al. [85]	2013	Case report	1 woman	The patient had severe relapse at 5 and 11 weeks after interrupting fingolimod The patient suffered from incomplete left hemianopsia and hypesthesia of the left arm; EDSS score was 3.5; brain MRI without gadolinium showed 14 new T2 lesions
Vukusic et al. [86]	2020	Clinical trials data and postmarketing setting	437 teriflunomide-exposed pregnancies	Pregnancy outcomes were comparable with those of the general population
Gold et al. [87]	2015	Preclinical, clinical trials, and postmarketing experience	2,898 patients with MS	Exposure to dimethyl fumarate was not associated with adverse pregnancy outcomes or fetal abnormalities

MS, multiple sclerosis; ARR, annualized relapse rate; DMTs, disease-modifying therapies; CIS, clinically isolated syndrome; GA, glatiramer acetate.

Table 2. A summary of studies on the effect of breastfeeding on MS

Reference	Year	Study design	Sample size	Main relevant findings
Achiron et al. [89]	2004	Retrospective study	108 pregnant women	Intravenous immunoglobulin is an effective treatment option to reduce MS relapses in pregnancy and postpartum There is no association between breastfeeding and postpartum relapses
Airas et al. [90]	2010	Prospective cohort study	61 women	The frequency of breastfeeding is low among patients with active disease before pregnancy Breastfeeding is not related to postpartum relapses
Runia et al. [91]	2015	Prospective and longitudinal study	MS = 43 Controls = 21	Postpartum relapses are not associated with breastfeeding
Jesus-Ribeiro et al. [92]	2017	Retrospective cohort study	127 pregnancies in 97 women	The rate of relapses reduced during pregnancy, mainly in the third trimester The rebound of MS occurred 6 months postpartum The most important predictor for postpartum relapses is relapsed during pregnancy DMTs had no effect on clinical and obstetric outcome Breastfeeding is not related to postpartum relapses
Portaccio et al. [93]	2011	Prospective cohort study	302 pregnancies in 298 women	The only predictor for postpartum relapses is the rate of relapses before and at pregnancy Breastfeeding is not associated with postpartum relapses
Haas et al. [94]	2007	Confirmatory, multicenter, randomized, stratified clinical trial	163 patients	Breastfeeding for >3 months is associated with lower postpartum relapses than in no breastfeeding
Langer-Gould et al. [95]	2009	Prospective cohort study	32 women with MS and 29 age-matched controls	The rate of postpartum relapses reduced with exclusive breastfeeding and suppression of menses
Hellwig et al. [96]	2015	Prospective cohort	201 women	Postpartum relapse occurred within the first 6 months in approximately 38% of those who did not breastfeed exclusively compared with than in 24% of those who decided to breastfeed exclusively for at least 2 months
Ragnedda et al. [97]	2015	International multicenter case-control study	1,586 Italians and 2,072 Norwegians	In Norway, MS status was not related to no/reduced breastfeeding; however, a statistically significant association was detected in Italy After stratification by gender, a strong significant association was detected in both Norwegian and Italian males only
Dalla Costa et al. [98]	2019	Retrospective cohort study	2055 patients with RRMS	Later age of MS onset in newborns was observed among babies delivered naturally and those breastfed for a minimum of 6 months The association is absent with a family history of MS
<i>MS treatment and breastfeeding</i>				
Cooper et al. [99]	2015	Case report	1 woman/child	Low infant exposure has been observed Brief use of IV methylprednisolone in lactating women with MS is recommended
Baker et al. [100]	2015	Case report	1 woman	Natalizumab transferral to maternal milk increased with time and subsequent administrations
MS, multiple sclerosis; DMTs, disease-modifying therapies.				

and the drop in interleukin levels [32]. Saraste et al. [18] also reported a decrease in the percentage of circulating natural killer cells during the last trimester of pregnancy. This increases again soon after delivery, which correlates with MS disease activity during and after pregnancy [18]. Additionally, the high level of sex hormones provided im-

mune modulation and neuroprotective effects during pregnancy [33].

Effect of Consecutive Pregnancies

A prospective assessment of the effect of consecutive pregnancies on the rate of relapse among 93 French wom-

en with MS showed that subsequent pregnancies had no negative effect on the relapse rate of MS [34]. The LeMS study also found no increase in the relapse rate among MS women with consecutive pregnancies [23].

Koch et al. [26] found that disability was not altered by parity and the number of pregnancies. A study by D'Amico et al. [35] of 86 women with MS found no relationship between the number of pregnancies and long-term disability. Another study found no association between the number of pregnancies and the time to reach disability but discovered that the rate of conversion from RRMS to SPMS was higher in monoparous than that in multiparous women [36].

Multiparity reduced the risk of progression in RRMS (but not PPMS) women compared with nulliparity in a cohort of 973 women from Belgium [37]. Masera et al. [38] reported a negative correlation between parity and disability score and observed an increase in the time to disability among parous women compared with nulliparous women [38].

Long-Term Progression and Conversion

In a study of 102 women with MS from Iran, the ARR 6 years after delivery was comparable with the ARR during pregnancy. There was no change in the average EDSS years after pregnancy [39]. Similarly, the findings of 2 large cohort studies by Karp et al. [40] indicated no relationship between pregnancy and long-term disability [40, 41]. A prospective study investigating 577 women who had carried one or more full-term pregnancies found no negative long-term effects of pregnancy [42].

Conversely, a protective effect has been observed. In a study of 55 pregnant women with MS, the mean EDSS in the postpartum period was 1.5, which was higher than that during pregnancy (EDSS: 0.7), suggesting that pregnancy has a protective effect on MS in terms of disability compared with the postpartum period [24]. In a cohort of 501 mothers with clinically isolated syndrome, pregnancy before or after clinically isolated syndrome had a preventive effect on clinically definite MS [43]. A Belgian study demonstrated a reduction in long-term disability in pregnant women [44]. Jokubaitis et al. [45] also demonstrated a protective effect of pregnancy in their large international retrospective cohort study ($n = 2,466$) with a lower long-term disability after 10 years.

One study reported some adverse effects of pregnancy on disease progression. Sixty pregnant women with radiologically isolated syndrome were compared with 53 nonpregnant patients with the same condition [46]. The conversion from the radiological into the clinical form of

the disease occurred faster in pregnant women; however, the groups were not comparable, and the conclusion may not be generalizable.

Obstetric Outcomes and Motherhood Decisions

Comparison of obstetric outcomes between women with and without MS by Cuello et al. [47] showed no significant differences. Furthermore, the pregnancy-related morbidity was similar. However, more assisted deliveries occurred in MS patients [47], as described by Dahl et al. [48, 49]. Another study retrospectively compared 432 births in mothers with MS to 2,975 births in healthy women. There were no significant differences between groups in obstetric outcomes such as type of delivery, mean gestational age, or birth weight [50]. Negative outcomes, including an increase in the rate of cesarean sections and reduced length and birth weight of the newborn of MS women, have been documented [19, 48, 49, 51, 52].

Fecundity in French women with MS did not differ between before and after the diagnosis of MS, whereas the miscarriage rate was similar to the general population. However, the average number of children per woman with MS was lower than that of the general population [53]. The effect of MS on motherhood decisions was evaluated in Portuguese women with MS. The decisions were not affected by the type of MS or frequency of relapses; however, several mothers believed that pregnancy would lead to worse disease outcomes. Therefore, after an MS diagnosis, mothers intended to have fewer pregnancies than before [54]. This could be related to a fear of transmitting the disease to offspring, especially if another family member is affected by MS. Furthermore, the lifetime probability of developing MS is 2% for a child with 1 parent with MS and 6–12% when both parents have MS. Other factors might include sexual dysfunction because of the disease or the cytotoxic effect of the medications, especially in progressive MS [33].

DMTs and Pregnancy

DMTs' initiation and drug choice is related to accessibility, safety, patient characteristics and comorbidity, and disease activity and severity. The pros and cons of continuing DMTs during pregnancy should be discussed with the patient to help her reach an informed choice [3].

The only licensed group B safe to use during pregnancy medication is glatiramer acetate (GA), as previously reported [55–58]. In a prospective multicenter cohort study, 423 pregnant women, exposed to GA or not, were followed, and GA was not related to an elevated risk of spontaneous abortion, preterm delivery, or low birth

weight [57]. However, some studies have suggested that there is an increase in the rate of assisted deliveries and birth defects [20, 58].

Most studies in the literature indicated the safety of continuing beta interferon (IFN- β) (Rebif[®], Avonex[®], Betaferon[®], Extavia[®], and Plegridy[®]) at least up until pregnancy [55, 59, 60]. Reports of IFN- β use during pregnancy showed no complications or harm to the fetus. However, the lower relapse rate during pregnancy means that IFN- β or GA during pregnancy may be unnecessary, although IFN- β takes several months to reach maximum effect after restarting [61, 62]. Some studies suggest that IFN- β increases the abortion rate; however, the rates were not significantly different from the general population comparators [63]. Conversely, early exposure in pregnancy has been linked to high assisted vaginal delivery rates, miscarriages, and birth defects [20, 58, 64].

A study of the exposure of women with MS in early pregnancy to natalizumab (Tysabri[®], NTZ, 2004) showed no risk of adverse pregnancy outcomes [65]. The MS Study Group of the Italian Neurological Society collected data on pregnancies occurring in patients receiving NTZ. Portaccio and others published several analyses, showing that pregnancy in MS patients did not protect from disease reactivation after NTZ suspension of <10 weeks before conception. Moreover, NTZ withdrawal in early pregnancy, compared with preconception, significantly reduced the relapse rate and disability accumulation [66]. This may be because NTZ is used in patients with active disease; therefore, the natural disease modification of pregnancy cannot compensate enough [30, 67–71].

Studies of NTZ exposure showed no negative prenatal or postnatal fetal health outcomes [72, 73]. The Italian group published several analyses, concluding that NTZ exposure in early pregnancy does not increase the risk of malformations; however, it increased the risk of spontaneous abortions in an Italian population [74]. Conversely, the risk of abortion associated with NTZ was within normal limits [69, 75]. Another controlled prospective study investigated fetal abnormalities associated with NTZ exposure in 101 German mothers with MS. No increase in major malformations and premature births was observed. However, miscarriage rates and low birth rates were significantly more prevalent than the controls among NTZ-exposed and disease-matched groups [76]. A systematic review and meta-analysis by Morris et al. [75] of women with MS treated with DMTs between January 2000 and August 2019 showed that the most common major congenital malformations reported were an atrial septal defect, polydactyly, and club foot; these are

among the most prevalent in the general population. The reviewers concluded that IFN- β , GA, and NTZ do not increase the risk of spontaneous abortions, preterm birth, or major congenital malformations.

NTZ is actively transported across the placenta only during the second and third trimesters. Furthermore, there is a slightly increased risk of hematological changes and suboptimal somatometric features among newborns [62, 77–81]. The Association of British Neurologists recommended that the last dose of NTZ be given at 34 gestational weeks and for treatment to resume early. To prevent MS relapses, NTZ should resume within 8–12 weeks of the last dose [62].

Fingolimod (Gilenya, 2011) is a sphingosine-1-phosphate analog that reduces the circulating lymphocyte count in the peripheral blood. The sphingosine-1-phosphate receptors play a role in the vascular formation, and the use of fingolimod is associated with vascular malformations and teratogenicity in animals [82]. The effect of fingolimod administered in early pregnancy has been associated with the developmental retardation and truncal ataxia in children [83]. The outcome of 66 pregnancies that occurred during the clinical development program of fingolimod in MS showed a higher rate of spontaneous abortions and, compared with the general population, the upper limit of abnormal fetal development [84]. Therefore, contraception is recommended with fingolimod in pregnancy. Fingolimod discontinuation is associated with MS rebound; therefore, replacement therapy is needed [85]. The UK consensus advice is that women with MS planning to become pregnant should stop fingolimod minimum 2 months before conception. In the event of an unplanned pregnancy, treatment should be stopped immediately, and the pregnancy should be closely monitored [62].

Teriflunomide (Aubagio[®], 2012) is a dihydroorotate dehydrogenase inhibitor that inhibits the proliferation of autoreactive B and T cells. It is teratogenic and is classified in the FDA category X. It has a very long enterohepatic circulation, and women who wish to conceive should stop it and undergo a washout period with cholestyramine or activated powdered charcoal [62]. There were no significant adverse findings in 437 pregnancies confirmed exposed to teriflunomide. Of the 222 with a known outcome, there were 21.2% spontaneous abortions and a stillbirth rate of 0.5%, consistent with the general population. Four birth defects were reported [86].

Dimethyl fumarate (Tecfidera[®], 2013) reduces the production and release of inflammatory molecules and has antioxidant properties. Although data on exposure in early

pregnancy are limited, postmarketing data showed no increased risk of fetal abnormalities or spontaneous abortion [87]. Women with MS on dimethyl fumarate are advised to use contraception while on treatment, and if they become pregnant, they should only continue treatment if the potential benefit justifies the risk to the fetus [62].

Alemtuzumab (Lemtrada[®], 2013) is a humanized monoclonal antibody against CD52, which causes a long-lasting depletion of lymphocytes. Contraception is recommended for 4 months posttreatment [88]. There is a 37% risk of developing autoimmune thyroid disease and less frequently others. The risk of other autoimmune diseases is increased for 4 years after treatment. In pregnancy, they can affect both the mother and fetus (e.g., neonatal thyrotoxicosis) [62].

Cladribine (Mavenclad[®]), an immunosuppressant drug which inhibits DNA synthesis and repair and is known as teratogen, has reproductive toxic effects and is embryo-lethal in animals and poses a serious potential risk to the fetus in humans. Women taking cladribine should continue contraception during and for minimum 6 months after treatment [62].

Ocrelizumab (Ocrevus[®]) and rituximab are anti-CD20 monoclonal humanized IgG antibodies. There are limited data regarding the use of ocrelizumab (Ocrevus) in pregnancy. It crosses the placenta and can potentially cause B-cell depletion in infants [62]. The manufacturers recommended contraception use during treatment and for 12 months after [62]. Transient peripheral B-cell depletion and lymphopenia have been reported in infants born to mothers exposed to rituximab during pregnancy. A study reported 90 live births, 22 premature births, 1 neonatal death after 6 weeks, 11 newborns with hematological changes, 4 newborn infections, and 2 congenital malformations [62].

Effect of Breastfeeding on MS

The effect of breastfeeding on MS remains debatable. Breastfeeding does not influence postpartum relapses [17, 89–92]. Airas et al. [90] reported a null association and found that the rate of breastfeeding among MS women was inversely correlated with disease activity before pregnancy. A low breastfeeding rate among MS patients compared with healthy controls has been reported [47]. The most important predictor for postpartum relapses is the rate of relapses during pregnancy [92, 93].

Breastfeeding, however, lowered the rate of postpartum relapses in some studies [94–96]. A multicenter randomized clinical trial that explored the effect of pregnancy on the rate of postpartum relapses concluded that

women with MS who breastfed for >3 months had a lower rate of postpartum relapses than those who never breastfed [94]. Hellwig et al. [96] studied women with MS who breastfed their babies exclusively for minimum 2 months after delivery. They observed a low relapse rate within the first 6 months postpartum [96]. Similarly, exclusive breastfeeding and the suppression of menses were associated with a drop in the postpartum relapse rate in one cohort study [95].

A large case-control multinational study of 3,658 participants in Norway and Italy evaluated the effect of breastfeeding on future MS [97]. A significant association between no or reduced breastfeeding (for <3 months) and MS was detected only in Italy with a 1.3 odds ratio (95% confidence interval, 1.09–1.7). However, the association was only significant in males, for developing MS in the future [97]. This could be related to the antiapoptosis features of prolactin and the reduction in tumor necrosis factor- α [32].

The possible effect of breastfeeding and the type of delivery on the onset of MS in newborns have been addressed in a cohort study that recruited 2,205 patients with a mean age of 29.4 years. Individuals delivered by cesarean section developed MS 5.2 years earlier than those delivered vaginally. Moreover, breastfeeding for ≥ 6 months was associated with a delayed onset of MS compared with formula feeding. These associations were observed among the patients without a family history of MS [98].

MS Treatment and Breastfeeding

Some studies have evaluated the secretion of MS medications in breastmilk. The majority of DMTs are not recommended during breastfeeding [62]. A case report has described the transmission of methylprednisolone through breastfeeding to the baby. However, brief treatment with methylprednisolone poses little risk of exposure to the newborn. The delay of lactation for 2–4 h after intravenous drug administration is recommended [99].

The transfer of natalizumab into breast milk has been reported. The infant dose is 1.7% of the weight-adjusted mother's dose [100]. The maximal infant relative dose at day 50 reached 5.3% with continued accumulation, which raises concerns regarding the fetal drug safety.

Conclusion

Pregnancy has an effect on reducing disease activity, especially in the third trimester. Whether pregnancy affects overall disability or MS disease progression is un-

clear. Similarly, the effect of breastfeeding on MS and the rate of postpartum relapses is undetermined.

Prepregnancy disease activity can predict a higher relapse rate during pregnancy and postpartum, and stabilization with DMTs is recommended. Family planning and pregnancy counseling must be considered when initiating and prescribing MS treatment. Current evidence reveals that pregnant women with MS are not at a high risk, and MS does not influence the mode of delivery or increase obstetric complications. Health education and reassurance for mothers regarding the protective benefits of pregnancy in MS should be adopted in multidisciplinary medical care involving primary health care specialists, neurologists, obstetricians, and gynecologists.

Statement of Ethics

The study is exempt from ethics committee approval because it is based on review of previously published literature.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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