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Review

Pregnancy and multiple sclerosis: Clinical effects across the lifespan

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ABSTRACT

Multiple sclerosis (MS) is commonly diagnosed in women of childbearing age. Having a greater understanding of the effects of pregnancy on the course of MS will lead to improved family-planning counselling for women. We found well-established evidence for a protective effect of pregnancy on relapse occurrence in historical cohorts. More recent studies suggest that the protective effect of pregnancy against relapse may be lost in those women with more active disease treated with high efficacy therapies. Furthermore, a strong body of evidence suggests that gravidity after diagnosis of MS does not lead to worse long-term outcomes. More contentious however, is whether pregnancy can delay a first episode of demyelination or a confirmed diagnosis of MS. This review provides a detailed analysis of the literature relating to the clinical effects of pregnancy on MS outcomes across a woman's reproductive lifespan.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS), of unknown aetiology. It is characterised by two sometimes overlapping clinical courses: relapsing MS, defined by inflammatory attacks (relapses) producing new or worsening neurological symptoms, and progressive MS, with sustained worsening of neurological function independent of relapse activity. MS is usually diagnosed between the ages of 20–50 years and women are three times more likely to develop MS than men [1]. Thus, the diagnosis is commonly made during a woman's reproductive years and issues relating to pregnancy are of significant clinical and pathophysiologic importance. Despite this, the question of whether pregnancy affects the course of MS is one of much debate.

Here, we review the literature relating to the clinical effects of pregnancy on MS outcomes during the lifespan. That is, the effect of pregnancy prior to MS onset, the changes in MS relapse activity during pregnancy, and the long-term disease outcomes for women with MS who have pregnancies.

2. Methods

We conducted comprehensive literature searches in the Pubmed database to retrieve studies that explored the effect of pregnancy on 1) MS/CIS onset, 2) long-term MS outcomes, or 3) relapse activity. The search included the terms: 'multiple sclerosis' or 'demyelination', 'pregnancy' or 'childbirth', 'onset' or 'risk', 'progression' or 'disability' and 'relapse'. Text terms were found in title/abstract and publications were limited to the English language. The screening process involved identifying only original research from the article titles and abstracts, then reviewing full-text manuscripts to select relevant articles. Further studies were included after searching the reference lists of full-text articles. The initial database search was performed in April 2018, and the search was updated in September 2018 to see if additional studies were available.

The exact Pubmed queries of the searches are shown below:

1) (multiple sclerosis[Title/Abstract] OR demyelination[Title/Abstract])) AND english[Language]) AND (pregnancy[Title/Abstract] OR childbirth[Title/Abstract]))) AND (onset[Title/Abstract] OR risk[Title/Abstract])
2) (multiple sclerosis[Title/Abstract] OR demyelination[Title/Abstract])) AND english[Language]) AND (pregnancy[Title/Abstract] OR childbirth[Title/Abstract])))))) AND (progression [Title/Abstract] OR disability[Title/Abstract])
3) (multiple sclerosis[Title/Abstract] OR demyelination[Title/Abstract])) AND english[Language]) AND (pregnancy[Title/Abstract] OR childbirth[Title/Abstract]))) AND relapse)

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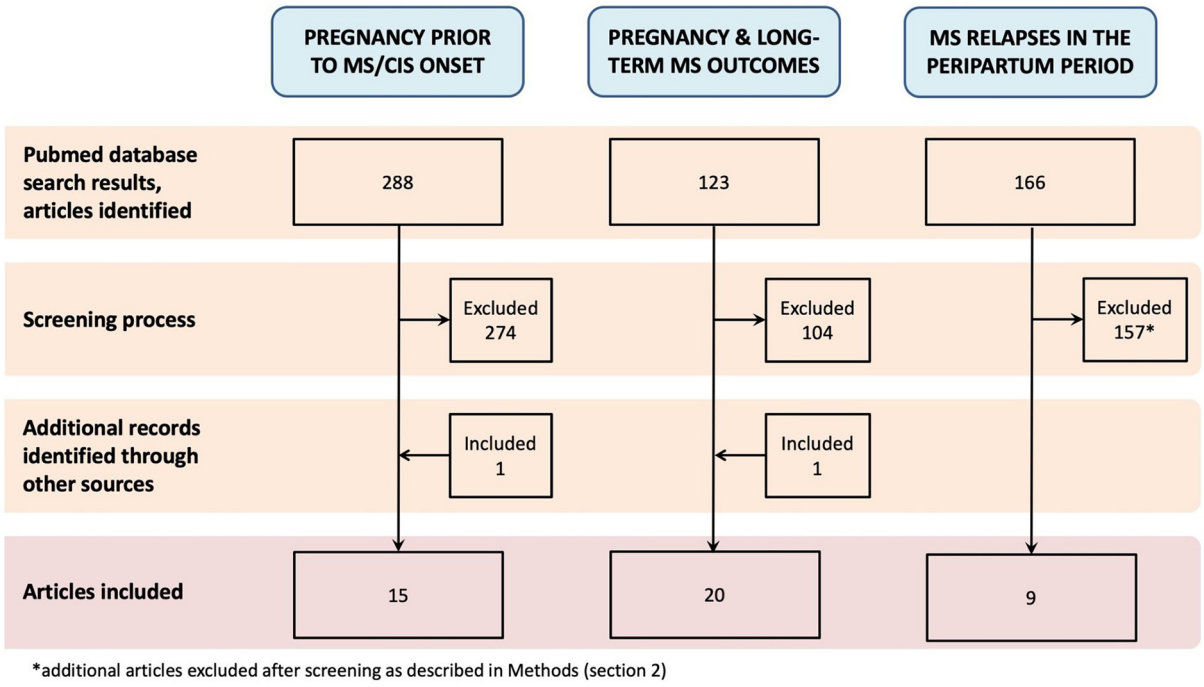

Fig. 1. Flow diagram of included studies.

The above searches yielded 288, 123 and 166 results respectively. We identified a total of 15 original papers that assessed the association between pregnancy and MS/CIS onset, and 20 papers that explored the relationship between pregnancy and long-term outcomes, all of which were included in our review. For the third search query on relapse activity, after the screening process, we selected a portion of studies for our literature review. This included the Pregnancy in Multiple Sclerosis (PRIMS) studies from the late 1990s [2,3], and studies published after a meta-analysis in 2011 [4]. An overview of the study selection process is summarised in the flow chart (Fig. 1), and the included studies are listed in Tables 1, 2 and 3.

3. Pregnancy and MS onset

Consensus is currently lacking regarding the effect of pregnancy on MS onset. Some of this disparity may be explained by study cohort composition and difficulty defining the exact onset of MS. The clinical onset of MS is defined as a Clinically Isolated Syndrome (CIS), marked by a single clinical episode of CNS demyelination without meeting the MS diagnostic criteria [5]. Preclinical onset of MS is now recognised in the form of Radiologically Isolated Syndrome (RIS), where MRI findings suggestive of MS are present in the absence of any history or clinical signs of MS [5]. Evolving definitions of RRMS [5–7] make interpretation of studies difficult as many would have included patients with RRMS as per latest criteria.

Studies to-date describe inconsistent findings, alternatively reporting no association, a harmful association or a beneficial association between pregnancy and MS onset. Most reports have focused on whether pregnancies reduce the risk of developing CIS, RIS or RRMS. However, some have additionally examined the impact of pregnancy timing and maternal age at first childbirth, as well as the effect of parenthood in males. Below, we summarise the outcomes of studies that have examined the impact of pregnancy on MS onset (Table 1). The term gravidity used in this review is defined as the total number of pregnancies and parity is defined as the number of births with gestational age $>$ 20 weeks (includes live births and stillbirths).

3.1. Evidence suggesting absence of an association between pregnancy and MS onset

Early studies generally concluded that there was no relationship between pregnancy and the onset of MS symptoms. In one of the earliest studies from the 1960s, Leibowitz et al. conducted a nationwide survey in Israel [8], and found no difference between MS cases and controls in the proportion who were gravidae or nulligravidae before MS onset. Extending upon this, two prospective pregnancy studies: the UK Family Planning Association study [9] and the USA Nurses' Health Study I and II study [10], assessed MS risk in women with 0, 1, 2, ≥ 3 or ≥ 4 children (Table 1). Both studies concluded that the number of live births had no effect on MS risk. This conclusion was supported by more recent case control studies, the UK General Practitioner Research Database study [11] and the USA MS Sunshine Study [12], both demonstrating that neither parity nor gravidity number impact MS/CIS risk.

Two large population-based case-control studies from Hedstrom et al. in Sweden [13] and Nielsen et al. in Denmark [14] included both females and males in their analyses. Each showed that in both sexes, parents had a reduced risk of MS compared to childless persons, arguing against a protective biological effect of pregnancy on MS risk. Nielsen et al. did, however, find that older maternal age at first live birth reduced the risk of MS [14]. Although, other studies found no such association between maternal age at first delivery and MS/CIS onset [10,12,13].

In exploring the relationship between timing of pregnancy and disease onset, Leibowitz and colleagues [8] noted that women with MS were more likely to have been pregnant in the year before MS onset. On the other hand, pregnancies ≤ 2 or ≥ 3 years prior to diagnosis were not associated with greater MS risk [8]. These findings were supported by others, concluding that MS risk was heightened in the 6 months postpartum [11,15], but that pregnancies ≤ 3 years [11] or > 5 years [13,14] before diagnosis were not associated with increased MS risk. Taken together, there is a suggestion that the postpartum period may be associated with a short-term increase in the risk of developing MS. This is consistent with immune system reconstitution and relapse rebound described in cohorts with clinically definite MS [2,16], although none

Table 1
Studies on the effects of pregnancy on CIS/MS onset.

Authors	Type of study	Participants	Methods	Results
STUDIES THAT SHOW NO ASSOCIATION BETWEEN PREGNANCY AND MS/CIS ONSET				
Leibowitz et al., 1967 [8]	Case-control	1963: 131 wwMS v 523 controls 1965: 122 wwMS v 244 controls	• Israel, nationwide questionnaire & interview 1963 & 1965 • Analysed pregnancies: live births, stillbirths, abortions	• No difference between patients and controls on gravidity, live births, stillbirths or abortions pre-MS onset • More patients than controls were pregnant 1y pre-MS onset
Villard-Mackintosh & Vessey, 1993 [9]	Prospective cohort	17,032 women ➔ 63 MS diagnoses	• UK, Oxford Family Planning Association (FPA) study • White married women aged 25-39y between 1968 and 1974 • Follow-up at least 25y • Pregnancy duration not defined	• Parity had no effect on MS onset (compared 0, 1, 2, 3+ children) • No association between time from last pregnancy and MS onset
Hernan et al., 2000 [10]	Prospective cohort	121,700 & 116,671 women ➔ 315 definite or probable MS diagnoses	• USA, questionnaire, Nurses Health Study (NHS) I & II • Follow-up 18y (NHS I) & 8y (NHS II) • Analysed pregnancies lasting ≥6 m	• Parity had no effect on MS onset (compared 0, 1, 2, 3, 4+ children) • Maternal age at first childbirth not associated with MS
Alonso et al., 2005 [11]	Case-control	106 wwMS v 1001 controls	• UK, General Practitioner Research Database (GPRD) • Aged > 50y between 1993 and 2000 • Follow-up at least 3y • Analysed pregnancies: full-term, preterm, stillbirths, abortions (spontaneous & induced)	• Gravidity had no effect on MS onset (compared 0, 1, 2+ pregnancies) • MS risk increased in the 6 m postpartum period
Nielsen et al., 2011 [14]	Case-control	6332 women and 3426 men with MS v 4.4 million controls	• Denmark, multiple nationwide registers including Danish MS Register • Aged 15-69y between1968–2005 • Analysed live births	• In both sexes, parents had a reduced risk of MS compared with childless persons (compared nulliparous v parous) • Risk of MS increased with time from the birth of the most recent child • Higher offspring number imparted more protection from MS (compared 1, 2, 3, 4+ children) • Older parental age at first childbirth reduced risk of MS • When date of MS diagnosis backdated by 5 years, MS risk not reduced in persons with children
Hedstrom et al., 2014 [13]	Case-control	1301 women and 497 men with MS v 3907 controls	• Sweden, questionnaire, hospital-based or private neurology clinics & national population register • Aged 16-70y • Analysed live births	• In both sexes, parents had a reduced risk of MS compared with childless persons (compared nulliparous v parous) • In both sexes, having children in the 5y prior to MS resulted in a reduced risk of MS • No association between offspring number and MS risk (compared 0, 1, 2, 3, 4 children) • Parental age at first childbirth not associated with MS
Langer-Gould et al., 2017 [12]	Case-control	397 women with CIS/MS v 433 controls	• USA, questionnaire, MS Sunshine Study • Aged ≥18 between 2011 and 2014 • Analysed parity & gravidity	• Parity & gravidity had no effect on CIS/MS onset (compared 0, 1, 2, 3, 4+ pregnancies) • Maternal age at first birth not associated with CIS/MS
STUDIES THAT SHOW A HARMFUL ASSOCIATION BETWEEN PREGNANCY AND MS/CIS ONSET				
Lebrun et al., 2012 [17]	Prospective cohort	60 women with RIS (7 pregnant v 53 non-pregnant)	• France • Mean follow-up 7y • Analysed childbirths	• Pregnant group had shorter time to CIS conversion • Pregnant group had higher mean number of new T2 lesions on MRI
Mohammedbeigi et al., 2016 [19]	Retrospective cohort	200 wwMS	• Iran, questionnaire & interview, MS Society in Isfahan • Aged 15-50y in 2014 • Pregnancy duration not defined	• Women with 1 or 2 pregnancies had earlier MS onset compared to nulliparous women (compared 0, 1, 2, 3+ children)
STUDIES THAT SHOW A BENEFICIAL ASSOCIATION BETWEEN PREGNANCY AND MS/CIS ONSET				
Runmarker & Andersen, 1995 [20]	Retrospective cohort	100 wwMS (definite/possible)	• Sweden, single site hospital database • Relapse onset MS, 15-49y, onset 1950–1964 • Follow-up at least 25y • Analysed full-term childbirths	• Risk of MS is more in nulliparous women compared with the expected frequency of nulliparity in the female population
Holmqvist et al., 2010 [22]	Retrospective cohort	770 wwMS	• Sweden, questionnaire, Swedish MS Register • Aged < 46y • Analysed childbirths	• Parity delays the age of CIS onset (compared nulliparous v parous)
Ponsonby et al., 2012 [23]	Case-control	216 women and 66 men with CIS v 542 controls	• Australia, questionnaire & interview, AusImmune study • Aged 18-59y between 2003 and 2006	• Higher offspring number reduces the risk of CIS in women, not men (compared 0, 1, 2, 3, 4, 5+ children) • Higher number of pregnancies and live births reduce the risk of CIS

(*continued on next page*)

Table 1 (*continued*)

Authors	Type of study	Participants	Methods	Results
			• Analysed pregnancies > 20 weeks, live births, liveborn children (offspring)	• No difference in time from last birth between patients and controls • Parental age at first childbirth not associated with CIS
Magyari et al., 2013 [21]	Case-control	1403 patients with MS (women & men) v 35,045 controls	• Denmark, multiple nationwide registers including Danish MS Registry • Aged 15-55y between 2000 and 2004 • Analysed childbirths	• Parity reduces risk of MS compared to nulliparity in women, not men (compared 0, 1, 2+ children) • This effect is only seen in the 5y preceding MS diagnosis • Parental age at first childbirth not associated with MS
Salehi et al., 2018 [24]	Case-control	399 wwMS v 541 controls	• Iran, questionnaire & interview, MS Society of Iran • Aged 15-50y between 2013 and 2015 • Analysed childbirths	• Parity reduces risk of MS compared to nulliparity • Higher offspring number reduces risk of MS (compared 0, 1, 2, 3, 4, 5+ children) • Older maternal age at first childbirth reduced risk of MS

MS, multiple sclerosis; v, versus; wwMS, women with MS; CIS, clinically isolated syndrome; RIS, radiologically isolated syndrome; MRI, magnetic resonance imaging.

of the above studies support a relationship between parity per se and risk of MS.

3.2. Evidence suggesting a harmful effect of pregnancy on MS onset

There have been two studies that identified a harmful effect of pregnancy on the risk of CIS (Table 1). Lebrun and authors are the only group to investigate the impact of pregnancy in 60 women with RIS [17]. In this French prospective cohort study, the pregnant group had a shorter time from first MRI to CIS conversion (15 months) than the non-pregnant group (36 months). Additionally, there were a higher number of new T2 lesions in the pregnant group during follow-up, consistent with a recent USA study that showed increased MRI lesion volumes postpartum in women with definite MS [18]. Further evidence has been presented by Mohammedbeigi et al. who retrospectively examined a cohort of 200 women with MS in Iran [19]. Here, the authors concluded that women with 1 or 2 pregnancies had an earlier age of MS onset compared to women with no pregnancies. No significant difference was found between women with ≥ 3 and no pregnancies.

3.3. Evidence suggesting a beneficial effect of pregnancy on MS onset

In 1995, Runmarker & Anderson found that the incidence of nulliparity was greater in women with MS relative to the general Swedish population [20]. This result was replicated by Magyari et al. in a large Danish cohort that found more women with MS were childless compared to controls [21]. Additionally, Holmqvist and colleagues published a study which demonstrated that parity delayed the age of CIS onset in Swedish women with MS [22].

An Australian study by Ponsonby [23], a Danish study by Magyari [21] and an Iranian study by Salehi [24] all found that CIS/MS risk decreased with increasing parity (Table 1). The Ponsonby AusImmune study found no relationship between timing of pregnancy and disease onset [23]. In contrast, Magyari et al. demonstrated that having children in the 5 years preceding MS diagnosis was favourable [21]. With respect to maternal age, only the Salehi et al. paper found that older maternal age at first childbirth reduced the risk of MS [24].

Interestingly, the Ponsonby study, correcting for other risk factors such as HLA-DRB1*15, smoking and vitamin D levels, found that parity reduced the risk of CIS only in women and not men [23]. In a further study by Magyari and colleagues, exposure to young children unrelated by blood in Danish households did not affect MS risk [25]. Both these studies argue for a biological rather than environmental benefit of pregnancy on MS onset.

3.4. Summary

The evidence that pregnancy affects MS onset remains inconclusive with approximately equal numbers of studies arguing for either a beneficial effect [20–24] or a net neutral effect [8–14]. Very few studies identify a heightened risk of developing MS [17,19]. The results of the RIS cohort [17] are discordant with the other studies and by the very nature of RIS, it is difficult to identify individuals with silent MRI activity. However, this subgroup may prove to be the most informative with respect to the impact of pregnancy on the development of clinically definite MS, and further investigation is warranted. We must also acknowledge that only one study to-date has had the capacity to adjust for genetic risk in these study populations [23], and it is likely that genetic predisposition in combination with other environmental factors (e.g. smoking, EBV and vitamin D/sunlight exposure) [26,27] have a greater impact on the manifestation of disease than pregnancy.

The problem of *reverse causality* is also likely a major contributor to the lack of consensus in the literature. That is, patients with premorbid MS may change their conceptive behaviour and avoid pregnancy, or have subclinical disease that affects reproductive activity [28,29]. Using CIS rather than MS as the endpoint in future studies may reduce

Table 2
Studies on MS during the peripartum period.

Authors	Type of study	Participants	Methods	Results
Confavreux et al., 1998 [2]	Prospective cohort	*254 wwMS:* 269 pregnancies Complete data on 241 women and 256 pregnancies	• 12 European countries, PRIMS study • Follow-up to 12 months postpartum • Used EDSS & ARR	• ARR reduced during pregnancy, most significantly in the third trimester, and increased in the first 3 months postpartum • EDSS worsened by 0.7 during 33 months of the study, no acceleration during postpartum period
Vukusic et al., 2004 [30]	Prospective cohort	227 full-term live births Longer term follow-up of original PRIMS study	• 12 European countries, PRIMS study • Follow-up to 24 months postpartum • Used EDSS & ARR	• ARR of pregnancy year (9 months of pregnancy and 3 months postpartum) similar to pre-pregnancy year • After first 3 months postpartum, ARR returned to pre-pregnancy levels • Early (3 month) postpartum relapses associated with higher baseline EDSS, higher ARR in pre-pregnancy year and during pregnancy
Finkelsztejn et al., 2011 [28]	Retrospective cohort	*128 wwMS:* 142 pregnancies 99 pregnancies (70%) exposed to DMT	• Brazil • Follow-up to 6 months postpartum • Used ARR	• ARR reduced during pregnancy, then increased in the first 6 months postpartum • ARR at 6 months postpartum lower than pre-pregnancy year
Hellwig et al., 2012 [29]	Retrospective & prospective cohort	335 pregnancies 119 pregnancies (36%) exposed to DMT	• Germany • Follow-up to 3 months postpartum • Used ARR	• ARR reduced during pregnancy, most significantly in the third trimester, and increased in the first 3 months postpartum • Postpartum ARR lower in DMT-exposed pregnancies compared to non-DMT exposed pregnancies
Neuteboom et al., 2012 [33]	Prospective cohort	*35 wwMS*	• Netherlands • Variable postpartum follow-up (range 8–24 months, mean 10 months) • Used EDSS & ARR	• ARR increased in first 3 months postpartum compared to third trimester of pregnancy • No difference in ARR between 9 and 12 month postpartum period and pre-pregnancy year • Postpartum ARR not associated with relapses in pre-pregnancy year or relapses during pregnancy • No change in EDSS during study period compared to pre-pregnancy year
Fragoso et al., 2013 [32]	Retrospective cohort	*132 wwMs:* 152 pregnancies 61 pregnancies (40%) with ≥8 weeks exposure to DMT 89 pregnancies (59%) not exposed to DMT	• Brazil, United Kingdom, Mexico, Argentina • Variable postpartum follow-up (range 2–280 months, mean ~4 years) • Used EDSS & ARR	• ARR reduced during pregnancy and increased in the first 6 months postpartum • Comparing DMT-exposed and non-DMT exposed pregnancies: similar ARR during pregnancy but DMT-exposed group had lower ARR in 6 months postpartum period • Mean EDSS at pregnancy onset higher in DMT-exposed group, but after 45 months postpartum, no difference in EDSS between groups • Increase in EDSS between pre-pregnancy and postpartum period observed in non-DMT exposed group, but not DMT-exposed group
Hughes et al., 2014 [15]	Prospective cohort	*674 wwMS:* 893 pregnancies 1.2% of pregnancies exposed to DMT	• International, MSBase registry • Follow-up from 2 years pre-pregnancy to 2 years postpartum • Used EDSS & ARR	• ARR reduced during pregnancy, most significantly in the third trimester, and increased in the first 3 months postpartum • ARR at 2 years postpartum similar to pre-pregnancy ARR • EDSS unchanged from pre-pregnancy through to postpartum period • Early (3 month) postpartum relapses associated with higher pre-pregnancy ARR and no DMT exposure pre-pregnancy
Portaccio et al., 2014 [31]	Prospective cohort	*345 wwMS:* 350 live births 74 women (21%) started DMT within 3 months postpartum (“early DMT”)	• Italy • Follow-up to 12 months postpartum • Used EDSS, ARR and disability progression (in 1st postpartum year)	• Postpartum relapses associated with EDSS ≥2.0 at pregnancy onset, higher number of relapses before and during pregnancy • Postpartum disability progression associated with higher number of relapses before and after delivery • Early DMTs after delivery did not predict postpartum relapses or disability progression
Alroughani et al., 2018 [37]	Retrospective cohort	*87 wwMS:* 99 pregnancies 90% of pregnancies occurred in women on DMT in the year preceding pregnancy	• Kuwait • Postpartum follow-up period not reported • Used number of relapses	• Relapses occurred in 17% of pregnancies • Higher rates of intrapartum relapse in women on fingolimod or natalizumab pre-pregnancy • Higher probability of intrapartum relapse with longer treatment washout periods

MS, multiple sclerosis; wwMS, women with MS; ARR, annualised relapse rate; EDSS, Expanded Disability Status Scale; DMT, disease-modifying therapy.

Table 3
Studies on the long-term outcomes of pregnancy on MS.

Authors	Type of study	Participants	Methods	Results
STUDIES THAT SHOW NO ASSOCIATION BETWEEN PREGNANCY AND LONG-TERM OUTCOMES				
Poser et al., 1979 [43]	Retrospective cohort	*446 wwMS*: 167 nulliparous, 222 parous pre-MS, 57 parous post-MS	• Germany • Mean disease duration 13y • Used Kurtzke DSS • Analysed live births	• No difference in disability between nulliparous, parous pre-MS & parous post-MS groups
Thompson et al., 1986 [44]	Retrospective cohort	*178 wwMS*: 48 nulliparous; 30 with 1 child, 100 with 2+ children; 23 parous pre-MS, 97 parous post-MS, 10 parous at MS onset	• UK • Mean disease duration (from CIS): 14y for parous women, 9y for nulliparous women • Used Kurtzke DSS & FSS • Analysed live births	• No difference in disability and number of pregnancies (0, 1, 2+) • No difference in disability between nulliparous, parous pre-MS and parous post-MS groups • Women with MS onset during pregnancy had less disability than other groups
Weinshenker et al., 1989 [45]	Retrospective cohort	*185 wwMS (includes probable)*: 69 nulliparous; 21 with 1 child, 50 with 2 children, 43 with 3 children; 74 parous pre-MS, 22 parous post-MS, 18 parous pre & post-MS	• Canada • Mean disease duration not stated (> 10y) • Used EDSS • Analysed childbirths	• No difference in disability and total number of term pregnancies (0, 1, 2, 3) • No difference in disability and timing of pregnancies relative to onset of MS (pre, post, pre & post)
Roullet et al., 1993 [46]	Prospective cohort	*125 wwMS*: 92 no pregnancies during follow-up (75 no pregnancies post-MS, 17 pregnant post-MS but before study onset), 33 pregnant during follow-up (32 term, 17 abortions)	• France • Mean follow-up 10y, variable disease duration between groups • Used EDSS & SPMS • Analysed term pregnancies, abortions (spontaneous & induced)	• No difference in disability between patients with pregnancies during follow-up, pregnancies post-MS & no pregnancies post-MS • No difference in proportion of SPMS between patients in the above three groups
Stenager et al., 1994 [47]	Prospective cohort	*29 wwMS*: 7 nulliparous, 10 parous pre-MS, 12 parous during or post-MS	• Denmark • Follow-up 5y, mean disease duration 8y • Used EDSS • Analysed childbirths	• Nulliparous women and women with pregnancies during or post-MS had increased disability at follow-up, but there was no change in disability among women with pregnancies pre-MS
Worthington et al., 1994 [48]	Prospective cohort	*15 parous wwMS* (14 post-MS) v 22 nulliparous wwMS (matched)	• UK • Follow-up to 3y postpartum, mean disease duration: 9y parous women & 8y nulliparous women • Used EDSS & FSS • Analysed live births	• No difference in disability between nulliparous and parous wwMS
Koch et al., 2009 [49]	Retrospective cohort	*277 wwMS (RRMS)*: 197 nulliparous, 80 parous post-MS (34 with 1 child, 46 with 2+ children)	• Netherlands • Median disease duration 17y • Used SPMS • Analysed full-term live births	• No difference in disability between nulliparous and parous post-MS groups • No difference in disability and number of pregnancies (0, 1, 2+)
Keyhanian et al., 2012 [53]	Retrospective & prospective cohort	102 women with RRMS who had only 1 live birth post-MS	• Iran • Mean disease duration 11y, mean follow-up 4y pre-partum & 6y postpartum • Used EDSS • Analysed full-term live births	• No difference in disability in years pre and post pregnancy
Ramagopalan et al., 2012 [50]	Retrospective cohort	*2105 wwMS:* 715 nulliparous, 911 parous pre-MS, 290 parous post-MS, 96 parous pre & post-MS	• Canada • Mean disease duration 15y • Used EDSS 6.0 • Analysed full-term live births	• No difference in time to disability between nulliparous, parous pre-MS, parous post-MS, parous pre & post-MS groups
Karp et al., 2014 [51]	Retrospective cohort	*1317 wwMS (RRMS):* 423 nulligravidae, 254 gravidae post-MS	• Canada • Median follow-up (from clinic entry or pregnancy): 3y for parous post-MS women, 7y for nulliparous women • Used SPMS & 1st documented EDSS 4.0 • Pregnancy duration not defined	• No difference in disability between nulligravidae and gravidae post-MS groups
Altintas et al., 2015 [54]	Retrospective cohort	*199 wwMS:* 455 pregnancies pre-MS, 103 pregnancies post-MS	• Turkey • Mean disease duration 13y • Used EDSS 6.0 & SPMS • Analysed childbirths, abortions (spontaneous & induced)	• No difference in time to reach EDSS 6.0 between patients with 1 pregnancy and patients with 2+ pregnancies[c] • Patients with 1 pregnancy had higher conversion rate from RRMS to SPMS than patients with 2+ pregnancies (although multivariate analysis show age and disease duration have stronger impact)
Bsteh et al., 2016 [52]	Retrospective cohort	*577 wwMS (RRMS):* 331 pregnancies post-MS	• Austria • Follow-up ≥10y post MS onset • Used EDSS 10y post MS onset (Kaplan-Meier estimates): categorised into mild, moderate and severe • Pregnancy duration not defined	• No difference in disability (mild, moderate, severe) and mean number of pregnancies
D'Amico et al., 2016 [55]	Retrospective cohort		• Italy	• No difference in disability and number of pregnancies (1, 2+)

(*continued on next page*)

Table 3 (*continued*)

Authors	Type of study	Participants	Methods	Results
		86 wwMS (RRMS): 56 with 1 child post-MS, 30 with 2+ children post-MS	• Baseline = 1st pregnancy post-MS; mean disease duration 4y at baseline, follow-up ≥7y post baseline • Used EDSS 4.0 & 6.0 • Analysed childbirths	
STUDIES THAT SHOW A BENEFICIAL ASSOCIATION BETWEEN PREGNANCY AND LONG-TERM OUTCOMES				
Millar, 1961 [56]	Prospective cohort	*377 wwMS*[a]: 139 single women, 109 married women with children post onset, 129 married women without children post onset	• Northern Ireland • Follow-up 10y, disease duration not stated • Used 6 grades of increasing disability (Hyllested 1956) • Analysed childbirths	• Married women with pregnancies post onset had less disability than single women
Verdru et al., 1994 [57]	Retrospective cohort	*200 wwMS (wheelchair dependent)*: 160 not pregnant post-MS (54 nulligravidae, 106 gravidae pre-MS), 40 gravidae post-MS	• Belgium • Disease duration not stated • Used progression = time from MS onset to wheelchair dependence • Pregnancy duration not defined	• Time to progression longer in patients with pregnancies post-MS compared to patients with no pregnancies post-MS
Runmarker & Andersen, 1995 [20]	Retrospective cohort	*133 wwMS (relapse-onset, includes probable)*: 55 nulliparous, 28 parous post-MS[b]	• Sweden • Follow-up at least 25y, disease duration not stated • Used Kurtzke DSS 6 & SPMS • Analysed full-term childbirths	• Time to SPMS longer in parous post-MS group compared to nulliparous group • Non-significant trend towards higher DSS 6 in nulliparous group
D'Hooghe et al., 2010 [58]	Retrospective cohort	*330 wwMS:* 80 nulliparous, 170 parous pre-MS, 61 parous post-MS, 19 parous pre & post-MS	• Belgium • Mean disease duration 18y • Used EDSS 6.0 • Analysed childbirths	• Reduced risk of progression in parous post-MS group compared to nulliparous group • Older age at progression for parous post-MS group compared to nulliparous group
D'Hooghe et al., 2012 [59]	Retrospective cohort	*973 wwMS (RRMS & PPMS)*: 198 with 0 pregnancies, 239 with 1 pregnancy, 524 with 2+ pregnancies[c]; 228 with no live births, 231 with 1 child, 502 with 2+ children[c]	• Belgium • Mean disease duration 19y • Used EDSS 6.0 • Analysed pregnancies and live births. Pregnancy duration not defined	• In RRMS patients, reduced risk of progression in women with ≥2 pregnancies/children compared to 0 pregnancies/children • No difference in disability for PPMS patients or if only 1 pregnancy/childbirth compared to 0 pregnancies/children
Masera et al., 2015 [60]	Retrospective cohort	*445 wwMS (relapse onset):* 261 nulliparous, 184 parous post-MS (125 had 1 pregnancy, 59 had 2+ pregnancies)	• Italy • Mean disease duration 14y • Used EDSS 4.0 & 6.0 • Analysed full-term childbirths	• Time to EDSS 4.0 & 6.0 longer in parous post-MS group compared to nulliparous group • Higher parity reduces risk of EDSS 4.0 (compared 0, 1, 2, 3, 4, 5+ children)
Jokubaitis et al., 2016 [61]	Retrospective cohort	*1830 wwMS (RRMS):* 226 women with 304 pregnancies in follow-up period (post-DMT)	• International • Baseline = 1st injectable therapy initiation[d]; median disease duration 4y at baseline, follow-up ≥10y post baseline • Used median EDSS change • Analysed term pregnancies (primary analysis), cumulative time spent pregnant (sensitivity analysis)	• Pregnant group had lower EDSS scores than non-pregnant group

MS, multiple sclerosis; v, versus; pwMS, patients with MS; wwMS, women with MS; DSS, Disability Status Score; FSS, functional systems scores; EDSS, Expanded Disability Status Scale; SPMS, secondary progressive MS; RRMS, relapsing-remitting MS; PPMS, primary progressive MS; DMT, disease-modifying therapy.

[a] Disseminated sclerosis.

[b] 24 women in this group contributed to nulliparous group and censored at pregnancy.

[c] Not specified if pre or post-MS onset, presumably both (pre & post-MS).

[d] Injectable DMT includes interferon-β or glatiramer acetate.

this interaction bias but it cannot be completely eliminated. Studies that included patients with CIS showed either no effect or a beneficial effect, although the Ponsonby et al. paper was the only one to exclusively use CIS patients [23]. Additionally, even with adequate matching to controls and adjustment for multiple factors, it is possible that unknown variables were independently affecting risk of MS or fertility [28].

4. MS and the peripartum period

In the last two decades, it has been well documented that during pregnancy, relapse rates in MS are significantly reduced [2–4,16] regardless of whether women have been on immunomodulatory therapy prior to conception [16,30,31]. The Pregnancy in Multiple Sclerosis (PRIMS) Study was the first large prospective observational study to analyse the effect of 269 pregnancies on relapse rates and disease progression [2]. Here, Confavreux et al. demonstrated a reduction in relapse rate across all trimesters in pregnancy, particularly the third trimester where there was a 70% reduction in relapse rate compared to the year pre-conception. This was followed by disease rebound in the 3 months postpartum for 28% of women, which subsequently returned to the pre-conception disease activity [2,3].

A meta-analysis that included 1221 pregnancies from 13 published studies similarly demonstrated that relapse rates significantly decrease during pregnancy [4]. The postpartum follow-up period varied among studies, but overall, there was a higher postpartum relapse rate compared to the year pre-conception [4]. It is worth noting that the PRIMS Study was completed just prior to the 'treatment era' when disease modifying therapies (DMT) became readily available. Nevertheless, even in the post-DMT era, these conclusions were replicated in a Brazilian study of 142 pregnancies (70% exposed to DMT at the time of

pregnancy) [30], a German study of 335 pregnancies (36% exposed to interferon-beta or glatiramer acetate) [31] as well as a large international study of 893 pregnancies (40% on DMT in the 2 years pre-conception) [16]. In all of these studies, there was a significant reduction in relapse risk during pregnancy; and in the latter two studies where postpartum data was collected, an increase relapse risk was seen in the early postpartum period [16,31]. Some of the studies analysing relapse rates in the peripartum period are summarised in Table 2.

Factors that predict an increased relapse rate in the postpartum period include: a high relapse rate pre-conception, relapses during pregnancy, and a higher baseline Expanded Disability Status Scale (EDSS) which is a widely used scale to quantify the severity of disability in MS [3,16,32]. Since the introduction and widespread use of DMTs for MS in the mid 1990s and 2000s, further studies have demonstrated that pre-conception DMT exposure is also protective against postpartum relapses [16,31,33].

It is important to note that these risk factors may not always be accurate at predicting relapse risk at an individual level. A prospective study in the Netherlands failed to show an association between relapses in the year pre-conception or relapses during pregnancy with postpartum relapse [34]. The PRIMS study identified 16% of patients who developed a postpartum relapse despite no prior relapse activity during pregnancy or the pre-conception period [3]. Furthermore, the majority of women in the postpartum period will remain relapse-free regardless of the risk factors described above [3,16].

Discussions on underlying biological mechanisms for the reduced relapse risk described in the above studies are beyond the scope of this article and will not be reviewed here. However, some authors have suggested that increased pregnancy hormones such as oestrogens and progesterone may shift the immune system towards an anti-inflammatory Th2 response [35–37]. Additionally, changes in CD56hi natural killer cells, regulatory T and B cells during pregnancy may be protective as opposed to the secretion of proinflammatory cytokines in the postpartum state, such as IFN-γ, IL-12 and TNF-α [35–37].

Notably, a recent study by Alroughani et al. identified a higher than expected relapse rate during pregnancy, but with similar postpartum relapse rates compared to previous reports [38]. In this study, 99 pregnancies were reported for 87 women, of which 24% of pregnancies were exposed to natalizumab, and 21% were exposed to fingolimod, both high-efficacy DMTs. Women who conceived on natalizumab had a greater baseline mean EDSS (2.5 ± 1.5) than those who conceived on other therapies (mean EDSS ranging between 1 and 1.5). It was found that long washout periods prior to conception in this cohort contributed to the observed heightened relapse rate [38]. Similarly, Portaccio et al. identified 37% of women who suffered a relapse during pregnancy after ceasing natalizumab [39]. Other cases have identified significant relapses in women during pregnancy who were considered to have stable disease whilst on natalizumab prior to pregnancy [40,41], suggesting that in more aggressive MS requiring potent DMT management, pregnancy alone may not be sufficient to reduce relapses related to drug-withdrawal rebound activity [40]. It has been postulated previously that one confounding factor prior to the DMT era is that women with more significant disability were less likely to have pregnancies. Now that MS can be better controlled with newer and more efficacious DMTs, women who previously would not have considered parenthood due to the aggressive nature of their disease are now more likely to attempt pregnancy, thus providing the likely explanation for the disparity between historical and more recent studies.

There has been a paucity of MRI studies in the peripartum period, but a recent study by Khalid et al. identified 16 women with RRMS who had pre-pregnancy and postpartum brain MRIs, with a mean of 4 months between pre-partum MRI and pregnancy, and mean 2 months between delivery and postpartum MRI [18]. The authors found increased T2 and T1 lesion volumes at the postpartum scan compared to the pre-pregnancy scan but no change in whole brain or cortical grey matter volume. Of the 16 women, only 38% were on pre-pregnancy DMT, with 2 patients on interferon-beta and natalizumab having 18 and 46 new gadolinium enhancing lesions respectively on the postpartum scan. The latter patient was reported to have severe intra- and postpartum relapses. Overall, 44% of women received steroids postpartum and of those on DMT pre-partum, 66% had steroid treatments compared to 33% of patients who were untreated pre-pregnancy [18]. It indicates a potentially more active group of patients becoming pregnant, which likely explains their MRI findings.

5. Long-term outcomes of pregnancy in MS

Historically, there was a widespread belief that pregnancy adversely affected the course of MS and female patients with MS were advised against pregnancy [42]. As described above, the seminal PRIMS study by Confavreux and colleagues played a major role in shifting perceptions of pregnancy in MS [2]. However, the effects of pregnancy on long-term disability are still contentious, and there are studies reporting either no effect or a beneficial effect on MS progression. In this section, we will discuss the associations between pregnancies occurring after MS diagnosis and long-term disability. We have classified studies into those that showed no association or a beneficial association between pregnancy and long-term outcomes (Table 3).

5.1. Evidence suggesting absence of an association between pregnancy and MS progression

Early retrospective cohort studies on women with MS in the 1970s and 1980s demonstrated no difference in disability outcomes between nulliparous women and women with childbirths after MS onset [43–45]. The latter group will henceforth be referred to as the 'parous post-MS' group. There were three subsequent prospective studies in the 1990s that also showed no difference in MS disability between nulligravidae and gravidae post-MS women [46–48], although these studies had smaller sample sizes and shorter follow-up periods than the retrospective studies. More recent retrospective studies in the last decade have demonstrated similar findings [49–52], including two large population-based studies from Canada of over 2000 women with any MS phenotype [50] and 1000 women with RRMS respectively [51] (Table 3).

All of the above negative studies compared nulligravidae women to gravidae post-MS women, with the exception of Bsteh [52], that assessed the relationship between mean number of pregnancies post-MS and the EDSS 10 years post MS onset. Keyhanian et al. used both a retrospective and a prospective cohort of women with RRMS who had only 1 live birth post-MS (ie primiparous), and found no difference in the pre-pregnancy EDSS and post-pregnancy EDSS of these primiparous women [53]. Two studies specifically investigated the relationship between pregnancy *number* and disability; and found no difference in disability between women with 1 pregnancy post-MS and those with ≥2 pregnancies post-MS [54,55]. The finding that pregnancy number did not affect the major disability milestones was also described in some of the aforementioned studies [44,45,49].

Of note, most of the contemporary studies included only women with RRMS, although, Ramagopalan [50] analysed all women with MS regardless of subtype. In terms of outcome measure for disability, the most commonly used outcome was time to EDSS 4.0 and/or 6.0, with time to SPMS or EDSS score being some of the other outcomes used. The mean disease duration or follow-up in these studies ranged from 5 to 17 years [43–55].

5.2. Evidence suggesting pregnancy delays MS progression

In contrast to the above studies, an early prospective cohort study in the 1960s found that married women who had children after diagnosis of disseminated sclerosis had lower grades of disability than single women [56]. This is one of the earliest studies to suggest an improved

prognosis for women with pregnancies post-MS onset, and it was followed up by two retrospective cohort studies in the 1990s [20,57] and another four retrospective studies in the last decade [58–61] that reached similar conclusions (Table 3).

Of these studies, two investigated the role of multigravida and both found that a higher gravida reduced the risk of MS progression compared to nulligravida [59,60]. In the earlier study by D'Hooghe, this was only true for women with RRMS who had ≥2 pregnancies but not those with a single pregnancy or those with PPMS [59]. In the papers which reported a beneficial role of gravidae on MS progression, the most common outcome measure for disability was time to EDSS 4.0 and/or 6.0, particularly studies from the last decade [58–60]. In the earlier studies, Verdru et al. used time from MS onset to wheelchair dependence (~EDSS 7.0) [57] while Runmarker & Andersen used time to SPMS [20].

The most recent study from Jokubaitis et al. included 1830 patients with RRMS and was one of the largest cohorts reported to-date. Here, their outcome measure was median EDSS change over a 10-year period from initiation of first-line injectable DMT, rather than time from MS onset [61]. This was a novel way to remove indication bias and include only patients on low-efficacy therapy. Untreated patients may represent a more benign group who have less disability and are potentially more likely to consider childbearing, as opposed to those on high-efficacy therapy who may have more aggressive disease and subsequently less consideration for childbearing. In the Jokubaitis et al. study, the parous post-MS group had lower EDSS scores than the non-pregnant group, although the effect size was modest, measuring a median 0.36-point lower EDSS score over a 10-year observation period relative to nulliparous women. When comparing the effect size of pregnancy relative to first-line therapy in this cohort, however, the study investigators reported that the therapeutic effect of pregnancy was more than four times greater than that of injectable DMT, even when accounting for confounders such as relapse activity [61].

5.3. Summary

The published literature to-date has more studies reporting no effect of pregnancy on MS disability than those reporting reduced disability or a delay in progression. Most of the studies reported at least 10 years follow-up or disease duration, which is a reasonable timeframe to assess the effect of pregnancy on disability outcomes, although a few of the studies showing no effect had < 10 years follow-up. In addition, most contemporary studies included only women with the RRMS subtype, and therefore, confounding by disease phenotype does not explain the disparity in study findings. Disability outcome measures were also similar in recent studies, i.e. the use of time to reach EDSS 4.0, 6.0 or change in EDSS. The majority of papers analysed childbirths or live births, and in the few papers that did include abortions, half reported no effect of pregnancy [46,54] and half demonstrated a beneficial effect [59,61]. In the studies that showed pregnancy delayed disability, a higher gravida was more beneficial [59,60].

One of the major limitations to the positive studies is that reverse causality may again play a role, similar to the papers on pregnancy and MS/CIS onset. Women with more aggressive disease may choose not to conceive due to concerns about their current symptoms, disability or choice of treatment during pregnancy. The Jokubaitis et al. paper did attempt to address this by using time from first-line injectable therapy as the baseline, and approximately 40% of reported pregnancies in this cohort were conceived on therapy [61]. However, unmeasured confounders may still impact all of the above study results, such as unmeasured environmental factors (smoking, vitamin D supplementation peripartum), as well as socioeconomic factors. Accounting for these may further help to elucidate the impact of pregnancy on long-term disability outcomes.

Overall, the above studies all concur that there are no harmful effects of pregnancy and therefore, we can be reassured that gravidity does not *increase* the risk of long-term disability in MS. Unfortunately, current evidence is not conclusive that pregnancies during MS *reduce* the risk of long-term disability.

6. Conclusions

The influence of pregnancy on the course of MS has been contentious for a long time, and the last few decades have brought about a dramatically increased understanding of pregnancy in MS which has greatly assisted our counselling of women with CIS and MS.

We now know that there is a well-established protective effect on MS relapses during pregnancy, most obvious in the third trimester for women with mild MS, with an increased relapse rate in the postpartum period for up to a third of all women, irrespective of disease severity. Unfortunately, it is still unclear if the risk of MS or CIS is reduced with increasing gravidity prior to MS onset, and if so, whether this is due to a biological or environmental effect. More work, in particular, large population-based studies are required to elucidate this relationship. Lastly, and arguably most importantly, there is sufficient evidence to reassure patients that gravidity during the course of MS does not lead to worse long-term outcomes. Further studies are needed to confirm if there is indeed a beneficial effect of pregnancy in slowing disability, as suggested by some papers.

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