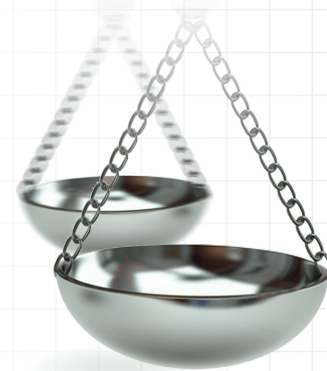




The effects of pregnancy on relapse rates, disability and peripartum outcomes in women with multiple sclerosis: a systematic review and meta-analysis

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Background: Although previous cohort studies of women with multiple sclerosis (MS) yielded a reduction in relapse rate during pregnancy, the effect size has not been quantified in a comprehensive manner. In addition, the effects on disability progression and peripartum outcomes have been controversial. The purpose of this work is to assess the effect of pregnancy on disease activity, and to assess the effects of MS on pregnancy as well. **Materials & methods:** We searched in PubMed, Cochrane Library and EMBASE for cohort studies dealing with the effects of pregnancy on relapse rates, disability progression and peripartum outcomes in women with MS. The evaluated outcomes were: changes in the annualized relapse rate (ARR) in pregnancy and puerperium, disability worsening compared with the year before pregnancy, and peripartum outcomes, which were compared with the ones of non-MS women. In the majority of cohorts included here, the women were not under disease modifying therapies during pregnancy. **Results:** We found 23 cohort studies measuring changes in the ARR during pregnancy and puerperium; 12 were prospective and 11 retrospective. In 17 cohorts there was significant reduction in the ARR during pregnancy compared with prepregnancy period. The pooled mean reduction in the ARR was -0.5 (95% CI: 0.67–0.38), $p < 0.001$, from 15 cohorts included in meta-analysis. In 18 cohorts the ARR increased in the 3-month puerperium relative to prepregnancy year period; the pooled mean increase in the ARR was 0.22 (95% CI: 0.11–0.33), $p < 0.001$, from 14 cohorts included in meta-analysis. Disability worsening was addressed in 18 cohorts, and in 14 of them there were no significant changes. Peripartum complications and obstetrical outcomes were assessed in 16 cohorts, of whom 13 were retrospective, without finding significant differences. **Conclusion:** Pregnancy is associated with lower disease activity, and puerperium with higher disease activity. Disability does not change significantly after pregnancy. The obstetrical outcomes are not very different from those of non-MS women in most cohorts.

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Keywords: annualized relapse rates • multiple sclerosis • pregnancy outcomes

Multiple sclerosis (MS) is a chronic immunomediated disease of the central nervous system in which inflammation, demyelination and axonal loss occur from early stages of the disease. It mainly affects young people between 20 and 40 years of age, with predominance in the female sex [1]. The average prevalence of MS in the world is 33/100,000 people, with significant variability among countries. Europe and North America have the highest prevalence (108 and 140/100,000 people), while Asia and sub-Saharan Africa have the lowest (2.1 and 2.2/100,000 people) [1,2].

Depending on the onset of symptoms and their clinical course, four main different phenotypes have been described: clinical isolated syndrome, relapsing-remitting MS (the most prevalent form), primary progressive MS and secondary progressive MS [1,3]. MS affects especially young women in the age of child bearing. This fact raises doubts and concerns in those patients with gestational desire, for the fear of possible complications of pregnancy, childbirth and postpartum. Before the first epidemiological studies, >50 years ago, it was thought that pregnancy was detrimental for MS women [4–6]. However, these misconceptions have changed on the light of retrospective

and prospective epidemiological studies. In addition, from an immunological viewpoint, pregnancy is considered an immunotolerant state, where the maternal immune system needs to adapt to the fetal allogeneic tissue [7], so it is expected that pregnancy may result in a decrease of autoimmune diseases activity [8]. Furthermore, in an incident cohort with 308 women, a reduced risk of MS onset was found in parous women compared with nulliparous ones [9]. However, pregnancy may also worsen or exacerbate other autoimmune diseases such as acute disseminated encephalomyelitis (ADEM) and neuromyelitis optica [10].

The interrelations between pregnancy and MS have been the focus of many published systematic reviews, but only one, published in 2011, reported a meta-analysis of disease activity changes during pregnancy and puerperium. The authors gave the overall relapse rates in prepregnancy period, pregnancy and puerperium, without statistical comparison [11].

The primary objective of this systematic review is to analyze the effects of pregnancy on the clinical course of MS (relapses and disability worsening) in a quantitative manner. The secondary objective is to analyze the effects of MS on pregnancy (peripartum complications, preterm birth and low birth weight).

Materials & methods

We made a search in PubMed, EMBASE and Cochrane Library for available evidence of the interrelations between MS and pregnancy without language restrictions, from 1967 to October 2019. We followed the PRISMA guidelines for systematic reviews. Different key words were used: 'pregnancy and multiple sclerosis', 'outcomes of multiple sclerosis in pregnancy', 'peripartum outcomes in multiple sclerosis women', 'relapse rate in pregnancy in multiple sclerosis' and 'long-term disability in pregnant women with multiple sclerosis'.

Study selection

The studies were selected by two authors. The main criteria for study selection were: to be cohort study, and to report either pregnancy outcomes in MS women or MS outcomes in pregnant women as primary end points. We did not include cohorts of women under disease modifying therapies (DMT) during pregnancy. We rejected articles based on case reports or small case series, those not dealing with outcomes in pregnant MS women, the ones not being longitudinal in nature and cohorts under DMT. A total of 1469 abstracts were screened; 1293 articles were excluded for analysis, and 91 were deemed eligible for analysis because they were longitudinal in nature and dealt with the interactions between pregnancy and MS. Finally, 64 papers were included for qualitative and/or quantitative analysis (see Flow diagram). The selection of studies was done by consensus between two appraisers.

Data extraction

We got the annualized relapse rate (ARR) in pregnancy and 3-month puerperium in comparison with either the ARR in the year before pregnancy or ARR in nonpregnant MS women, depending on the design of the study. For meta-analysis we included studies reporting the ARR before, during pregnancy and in the 3-month postpartum, giving also either standard deviation (SD) or standard error. Disability progression was based on longitudinal assessments by means of the expanded disability status scale (EDSS). We assessed as well the influence of MS on pregnancy outcomes and peripartum complications (preterm delivery, low birth weight, infections, miscarriages, influence of epidural anesthesia, breastfeeding and assisted reproductive techniques [ARTs]).

Pooled changes in ARR before pregnancy, during and after pregnancy were calculated with a fixed effects and a random effects model meta-analysis. We used the MedCalc Statistical Software version 19.1.5 (MedCalc Software bv, Ostend, Belgium; <https://www.medcalc.org>; 2020). Retrospective and prospective studies were also analyzed separately. Publication bias was assessed by means of funnel plots, which depicts the symmetric/asymmetric position of positive and negative studies in each side of the midline. The more symmetric the position of the studies, the less the risk of publication bias.

Heterogeneity was assessed by Q-test and inconsistency index (I^2). In the event that heterogeneity was significant (I^2 being $> 50\%$), it will be addressed with subgroup analysis and by calculating the rate ratios with the number of relapses, and person-years follow-up.

Results

We found 23 longitudinal studies measuring the changes in the ARR [12–34]; 12 of them were prospective [15,17–19,21–23,26–28,32] and 11 were retrospective [12–14,16,20,24,25,29,31,33,34]. In Table 1 are given the main characteristics of every study: number of patients, design, follow-up period and main outcomes. With regard to MS phenotypes, some

Table 1. Cohort studies dealing with the risk of relapse in multiple sclerosis pregnant women.

Study (year)	Cohort type	N of patients	Outcomes	Ref.
Ghezzi (1981)	Retrospective, 21 months	119 pregnant vs 100 nonpregnant MS women	ARR increased from 0.33 to 0.38, up to 1.01 in postpartum	[12]
Korn-Lubetzki (1984)	Retrospective, 12 months	338 women and 199 pregnancies	ARR decreased from 0.29 to 0.14; increased ARR in postpartum to 0.82	[13]
Frith (1988)	Retrospective, 15 months	52 women and 85 pregnancies	ARR decreased from 0.53 to 0.18; down to 0.13 in postpartum	[14]
Bernardi (1991)	Prospective, 15 months	52 women and 66 pregnancies	ARR decreased from 0.65 to 0.10; increased in postpartum to 0.79	[15]
Nelson (1988)	Retrospective, 9 months after delivery	191 pregnancies	AAR: 0.13 unchanged, but increased in postpartum to 0.4	[16]
Roulet (1993)	Prospective, up to 6 months postpartum	33 women and 49 pregnancies	ARR increased from 0.51 to 0.61; NS; increased in postpartum to 1.61	[17]
Sadovnick (1994)	Prospective, 15 months	47 women, 69 pregnancies and 64 controls	ARR decreased from 0.57 to 0.42; NS; rose to 0.75 in postpartum	[18]
Confavreux (1998)	Prospective, 12 months postpartum	254 women with 269 pregnancies	ARR decreased from 0.7 to 0.2; rose in postpartum to 1.2	[19]
Salemi (2004)	Retrospective, mean disease duration 16 years	70 women with 98 pregnancies, vs 281 nonpregnant	ARR decreased from 0.48 to 0.36; rose to 0.84 in postpartum	[20]
Airas (2010)	Prospective, 6 months postpartum	61 women	ARR decreased from 0.82 to 0.40; rose to 1.40 in puerperium	[21]
Portaccio (2011)	Prospective, 1 year after delivery	298 women, 302 pregnancies	ARR decreased from 0.4 to 0.12; rose to 0.55 in postpartum	[22]
Keyhanian (2012)	Prospective, 6 years after delivery	102 women	ARR decreased from 1.06 before pregnancy to 0.35; rose to 1.02 in postpartum	[23]
Hughes (2014)	Retrospective, 24 months postpartum	674 women, 893 pregnancies	ARR decreased from 0.32 to 0.20; rose to 0.61 in postpartum	[24]
Karp (2014)	Retrospective, 3 years	254 pregnant vs 423 nonpregnant women	ARR decreased in pregnant women; rate ratio: 0.67 (0.49–0.92)	[25]
Fares (2016)	Prospective, 5 years	29 pregnant women, 64 pregnancies	ARR decreased from 0.17 to 0; rose to 0.2 at 1 year of postpartum	[26]
Benoit (2016)	Prospective, 1 year	161 women, 93 with two pregnancies each	ARR decreased from 0.52 to 0.24; rose to 1.33 in postpartum	[27]
Cuello (2017)	Prospective, 1 year	35 MS women and 40 pregnancies, vs 56 healthy women	ARR decreased from 0.5 to 0.3; rose to 0.4; NS	[28]
Jesus-Ribeiro (2017)	Retrospective, 33 months	97 women, 127 deliveries	AAR decreased from 0.6 to 0.3; up to 0.98 in puerperium	[29]
Lai (2018)	Prospective, 1 year after delivery	14 women and 15 pregnancies	ARR decreased from 0.46 to 0.07; rose to 0.55 in postpartum	[30]
Houtchens (2018)	Retrospective, 1 year postpartum	2158 women	ARR decreased from 1.47 to 0.87; rose to 2.56 in postpartum	[31]
Bsteh (2018)	Prospective, 2 years	239 women and 387 pregnancies	ARR decreased from 0.38 to 0.18; rose to 0.64 in postpartum	[32]
Alroughani (2019)	Retrospective, up to 3 months postpartum	132 women, 164 pregnancies	ARR increased from 0.1 to 0.2	[33]
MacDonald (2019)	Retrospective, up to 6 months postpartum	1168 women	NS change, from 0.5 to 0.4; in postpartum 0.5	[34]

ARR: Annualized relapse rate; MS: Multiple sclerosis; NS: Not significant.

studies did not specify the number/percentage of patients with relapsing-remitting or progressive form. According to several studies the percentage of patients with relapsing-remitting form ranged from 87.4 to 96% [19,24,27,28,31,33]. In other studies all patients had relapsing remitting (RR) forms [16,17,20,25,29,32].

With regard to DMT, most cohorts included women not under treatment during pregnancy. In five cohorts the percentage of women exposed to DMT were: 1.2 [24], 3.7 [33], 15.3 [25], 17 [31] and 34% in a small cohort of 35 women [28].

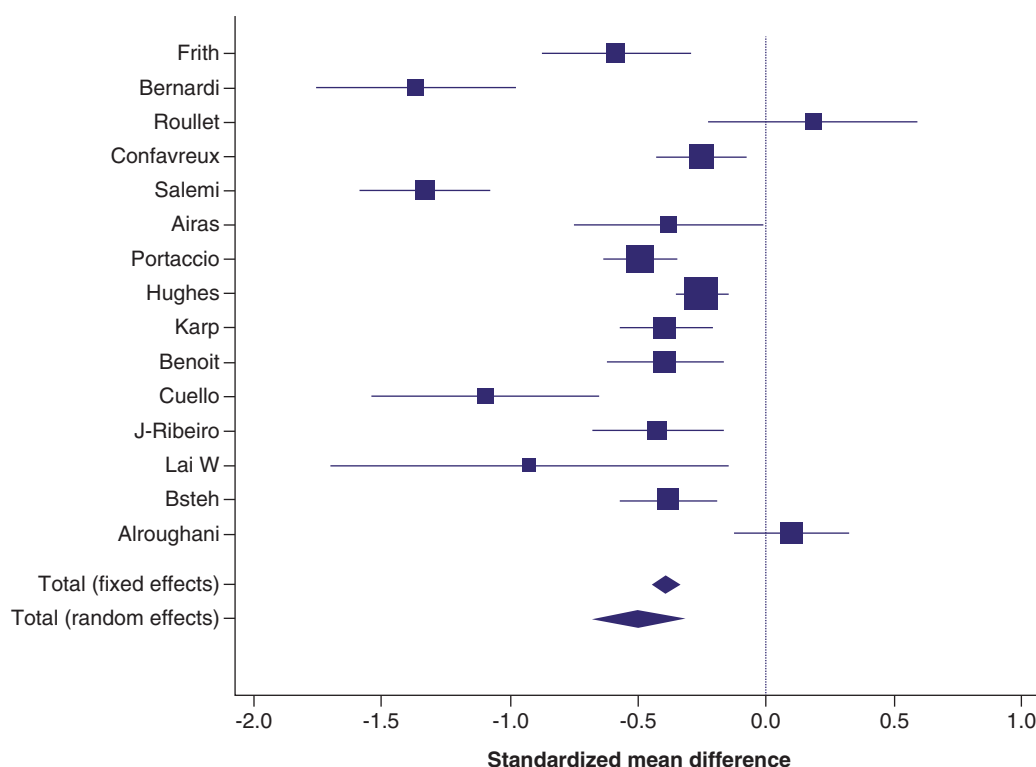


Figure 1. Meta-analysis from cohort studies giving the mean change in the annualized relapse rate before pregnancy/pregnancy. Fixed effects model. Pooled SMD: -0.39 (95% CI: 0.44–0.34); $p < 0.001$. Random effects model. Pooled SMD: -0.5 (95% CI: 0.67–0.38), $p < 0.001$. I^2 : 89.7%. I^2 : Inconsistency index; SMD: Standardized mean difference.

Changes in the ARR

In 16 studies, the ARR decreased significantly in pregnancy (see Table 1), especially in the third trimester. The ARR were unchanged or not significant in four studies [16,18,28,34]. In two cohorts the ARR increased mildly, without statistical significance [12,17]. Only in one of the studies the ARR increased significantly from 0.10 to 0.20, as a consequence of DMT withdrawal before pregnancy [33]. The comparisons were made with a control group of nonpregnant MS women in five studies [12,18,20,25,28], and with the patients as self-controls in the year before pregnancy in all of the studies. In meta-analysis we included the papers giving the mean number of relapses and SD. One of the studies with small number of cases and high percentage on DMT during pregnancy was also excluded from meta-analysis [28]. The pooled mean change in the ARR from the preconception period to pregnancy was -0.5 (95% CI: 0.67–0.38) from 15 cohorts included in meta-analysis, which was significant (see Figure 1). For retrospective studies it was -0.47 (95% CI: 0.79–0.15), and -0.47 (95% CI: 0.65–0.30) for prospective studies; $p < 0.001$ for both analyses. Heterogeneity was present in the three analyses (I^2 being $>75\%$). Funnel plot shows also heterogeneity, without bias of publication (Figure 2).

In 19 studies, the ARR increased in the 3-month puerperium compared with the year before pregnancy. In one study the rate decreased [14], in another one it did not change [34] and in two studies no information was given on puerperium relapses [24,33]. Mean relapse number and SD were given in 14 studies. The pooled mean change in ARR between prepregnancy period and 3-month puerperium from these 14 studies was 0.22 (95% CI: 0.11–0.33), $p < 0.001$ (Figure 3), and it was similar for prospective and retrospective studies. In this analysis, heterogeneity was lower than before (I^2 : 73%). In the funnel plot of Figure 4, the bias of publication cannot be ruled out.

From the evidence presented in all of these studies, we can infer with confidence that pregnancy is associated with a decrease in the ARR in MS women relative to the preconception period, and with an increase in puerperium, especially in the 3 months after delivery. According to funnel plots, publication bias cannot be excluded.

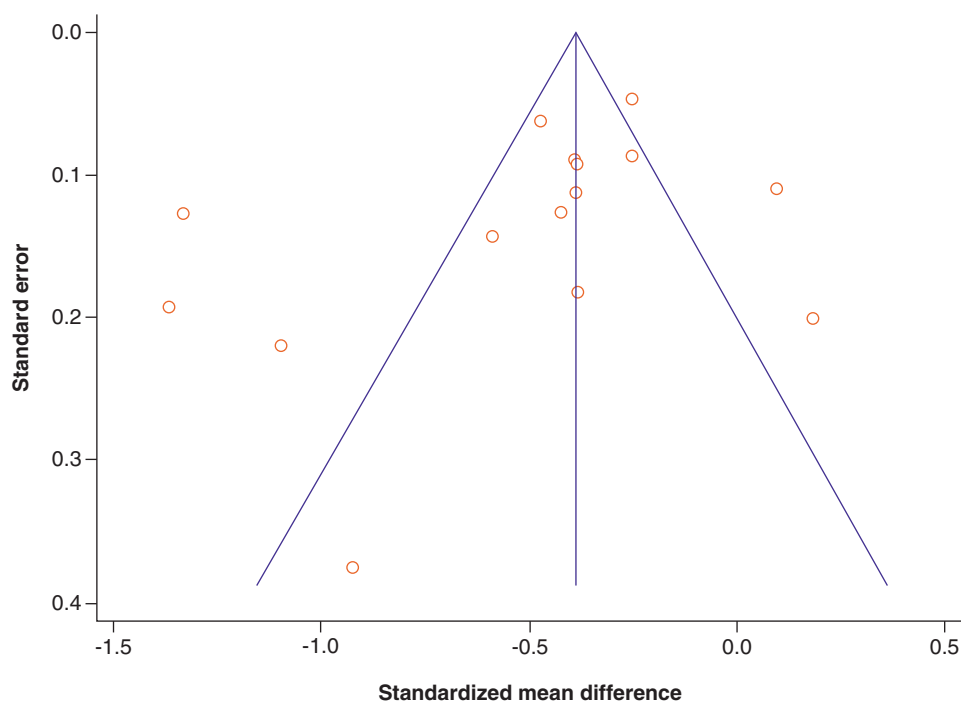


Figure 2. Funnel plot of meta-analysis showing variability of effect size among studies. Several points out of the triangle in both sides. Small risk of publication bias, as there were studies in both sides of the midline.

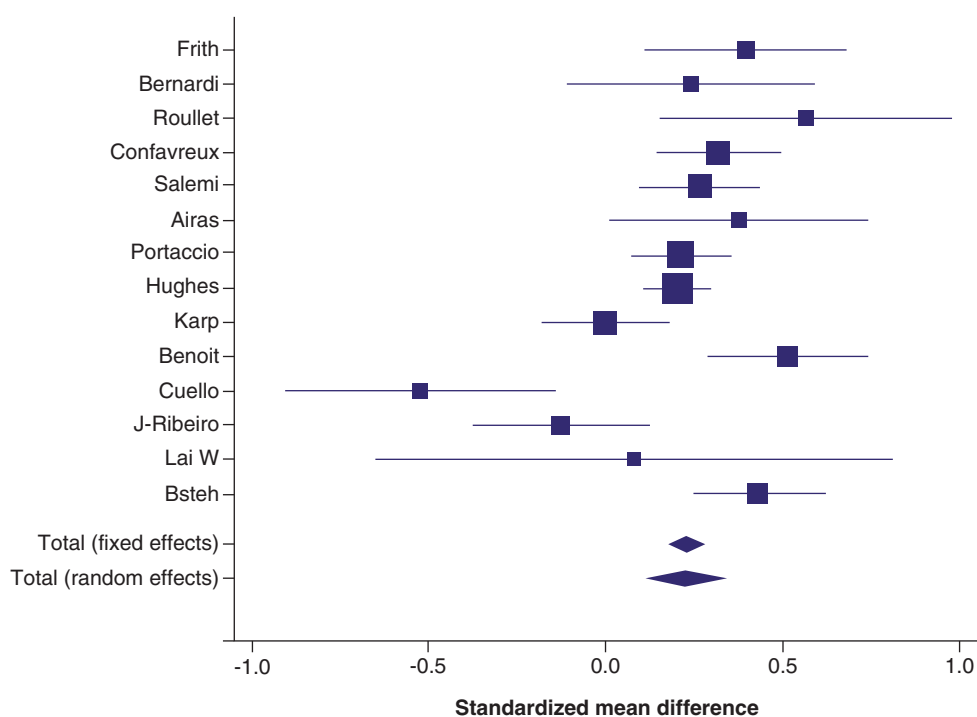


Figure 3. Meta-analysis from cohort studies giving the change in the mean annualized relapse rate pregnancy/puerperium. Fixed effects model. Pooled SMD: 0.22 (95% CI: 0.17–0.28). Random effects model: Pooled SMD: 0.22 (95% CI: 0.116–0.336. I^2 73% (53–84%). I^2 : Inconsistency index; SMD: Standardized mean difference.

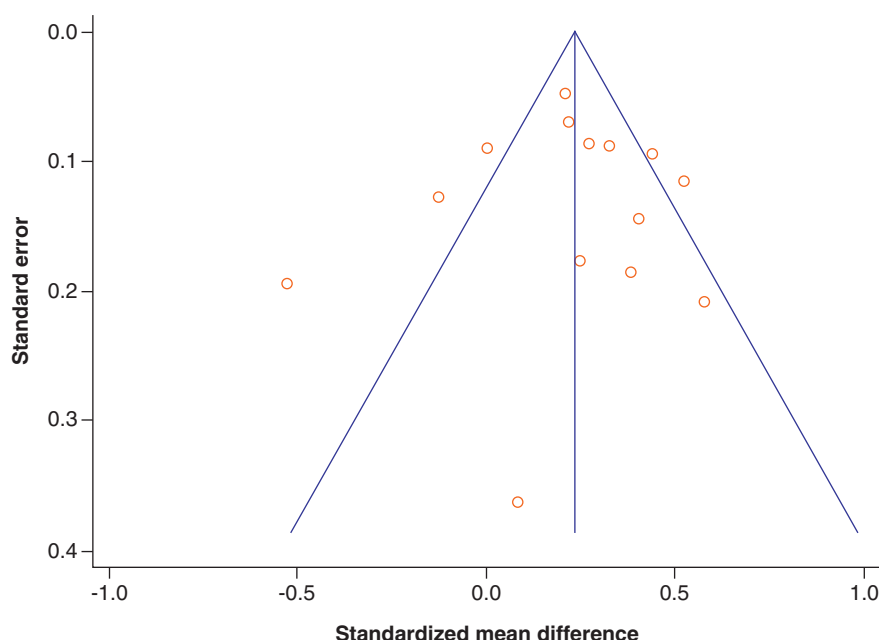


Figure 4. Funnel plot of meta-analysis of the increase in annualized relapse rate from pregnancy to puerperium. Symmetric distribution of studies, with some outliers. Small risk of publication bias.

Disability worsening

The papers dealing with disability worsening are given in Table 2. Among 18 studies, seven were prospective [9,17,23,28,30,35,36] and 11 were retrospective [24,25,37–45]. In 14 studies there was no significant disability worsening after pregnancy; in three the risk of disability worsening decreased [35,42,43] and in one it increased [30]. In the cohort of Karp *et al.* [25], the rate of irreversible disability at 5 and 10 years was similar, but the rates of transition to progressive forms were higher in pregnant MS women than in nonpregnant MS women. Thus, pregnancy does not increase the risk of disability worsening in MS women.

Obstetrical outcomes

Seventeen studies focused specifically on the effects of MS on pregnancy with peripartum outcomes; 14 were retrospective [5,37–39,46–55] and three were prospective [28,56,57]. In 12 of them, there were no significant differences in preterm deliveries, congenital malformations, miscarriages, stillbirths and abortions (see Table 3). In two retrospective cohorts, there was an increased number of infections and preterm deliveries [34,50], an increased number of preterm deliveries and low birth weight [47], low birth weight in another one [46], and anemia and rehospitalization in one study [52] (see Table 3). The evidence found here is not strong enough to draw definitive conclusions, but the available data are reassuring in this respect. Other pregnancy-related factors influencing the clinical course of MS are breastfeeding and analgesia. There is remarkable evidence that breastfeeding does not have influence on relapse recurrence, peripartum outcomes and long-term prognosis of MS [16,21,22,29,36,58]. Epidural analgesia has not been associated either with negative outcomes in puerperium [29,36,48,55,59].

What about ART in MS women? Some small case series yielded an increased risk of relapse after ART [60–64]. In a Bostonian cohort with 22 ART cycles, the relapse rate was not higher after ART than before, but in a meta-analysis of the same authors there was found an increase in the ARR after ART of 0.92 compared with the year before ART, but with small effect size ($p = 0.01$) [64].

In this systematic review, we did not analyze pregnancy outcomes on women exposed to DMT.

Subgroup analysis, sensitivity analysis & interactions

We compared prospective with retrospective cohorts, taking into account the number of patients included in each study. With regard to relapse rate changes in pregnancy months, there is an agreement between prospective and retrospective cohorts on the decreased ARR. The increased ARR in puerperium is found in most studies, in retrospective and in prospective studies as well. The ARR change varied among studies, but with the generic inverse

Table 2. Cohort studies focused on disability worsening in pregnant multiple sclerosis women.

Author (year)	Cohort and follow-up	N of patients	OR/RR and 95% CI, other measure	Ref.
Poser (1983)	Retrospective, 6 months after delivery	91 women and 129 pregnancies, vs 64 MS controls	Progression index not different from controls	[37]
Thompson (1986)	Retrospective	178 women	No differences in long-term disability	[38]
Weinshenker (1989)	Retrospective	185 women	No differences in long-term disability	[39]
Roullet (1993)	Prospective, 10 years	33 women with 49 pregnancies	Variation of EDSS: NS Transition to SPMS: 1.38 (0.68–2.78); NS	[17]
Verdru (1994)	Prospective, 18 years	200 women	Mean time to wheelchair: 18.6 years for pregnant, and 12.5 for nonpregnant women [†]	[35]
Runmaker (1995)	Prospective	308 women	Time to reach 6 points on EDSS: NS	[9]
Vukusic (2006)	Prospective, 2 years postpartum	254 women	No differences in disability progression	[36]
Koch (2009)	Retrospective, 17 year disease duration	277 women	No differences in disability progression	[40]
Ramagopalan (2012)	Retrospective, 15 year disease duration	2105 women	No effect on time to reach 6 points in EDSS	[41]
D'Hooghe (2012)	Retrospective, disease duration 19 years	973 women	Lower risk of disability progression with two or more pregnancies; OR: 0.66 [†]	[42]
Keyhanian (2012)	Prospective, 6 years after delivery	102 women	No influence on disability progression	[23]
Karp (2014)	Retrospective, 5- and 10-year outcomes	254 pregnant vs 423 nonpregnant women	– 5 Year: irreversible disability: 0.82 (0.36–1.88) – 10 Year: 4.14 (0.89–19.22) – 5 Year transition to SPMS: 2.33 (1.03–5.26) [†] – 10 Year transition to SPMS: 4.33 (1.1–19.96) [†]	[25]
Hughes (2014)	Retrospective, 24 months postpartum	674 women, 893 pregnancies	EDSS unchanged	[24]
Masera (2015)	Retrospective, 14 year disease duration	445 women, 184 parous	Lower risk of disease progression; OR: 0.55 [†] to reach an EDSS of 6 points	[43]
Altintas (2015)	Retrospective, 13 year disease duration	199 women and 558 pregnancies	Time to reach 6 points on EDSS not significant	[44]
D'Amico (2016)	Retrospective, 7 year observation period	86 women with one or more pregnancies	No differences in time to reach 4 or 6 points in EDSS	[45]
Cuello (2017)	Prospective, 2 years after delivery	35 MS women and 40 pregnancies, vs 56 healthy women	No significant changes in EDSS score	[28]
Lai (2018)	Prospective, 1 year after delivery	14 women and 15 pregnancies	Mean EDSS 1 year after delivery 1.5 (SD: 1.72) vs 0.77 (SD: 1.35) before pregnancy; p = 0.045	[30]

[†] Means significant.
[‡] Means significant difference.
EDSS: Expanded disability status scale; NS: Not significant; OR: Odds ratio; SD: Standard deviation; SPMS: Secondary progressive multiple sclerosis.

variance method, the results of meta-analysis were similar, and with higher degree of heterogeneity. Withdrawing cohorts before the DMT era (studies published before 1995) from analysis did not result in a lower degree of heterogeneity. The same happened when small cohorts were excluded from analysis. Given that the cohorts come from different countries in the world, heterogeneity may be explained by interactions by country.

With a different approach and other metric (rate ratios), another meta-analysis was conducted from 20 cohorts reporting the number of relapses and person-year follow-up [12–22,24,26–30,32–34] (see Table 4). In the preconception period, 2296 relapses happened for 5815 person-years, in comparison with 772 relapses for 3158 person-years in pregnancy; rate ratio: 0.61 (95% CI: 0.56–0.67). In puerperium, 1378 relapses were reported for 2380 person-years; the rate ratio preconception/puerperium was 1.46 (95% CI: 1.37–1.56); the rate ratio pregnancy/puerperium was 2.38 (95% CI: 2.16–2.59). The pooled incidence rate difference between preconception period and pregnancy was -0.15 (95% CI: 0.17–0.12), and 0.18 (95% CI: 0.15–0.21) between preconception and postpartum period, but heterogeneity remained. With this approach, we have the advantage of including more cohorts in the meta-analysis, but the main caveat is that the follow-up period of prepregnancy and puerperium varied considerably across cohorts, so heterogeneity could be explained by this fact. In general terms, the results are equivalent with both methods, which increases robustness of the conclusions.

In terms of disability worsening, most prospective and retrospective studies pointed to nonsignificant differences (Table 2). In nine out of 11 retrospective studies including a total of 4039 women, pregnancy was not associated with

Table 3. Cohort studies addressing pregnancy outcomes.

Author (year)	N of MS patients	Results	Ref.
Liebowitz (1967); retrospective	131 MS patients vs 523 controls	No differences in live births, stillbirths or abortions	[5]
Worthington (1994); prospective	15 women vs 22 nonpregnant MS women	No effect on pregnancy No effect on peripartum children outcomes	[56]
Poser (1983); retrospective	91 pregnant women vs 64 MS nonpregnant women	No effect on the risk of congenital malformation	[37]
Dahl (2005); retrospective	461 women and 649 deliveries vs 2 million control births	Lower birth weight compared with controls	[46]
Chen (2009); retrospective	174 MS women vs 1392 controls	Increased risk of preterm delivery and low weight	[47]
MacDonald (2019); retrospective	3875 pregnancies vs controls	Increased risk of infections and preterm delivery	[34]
Hanulikova (2013); retrospective	66 women vs controls	No differences in preterm deliveries or miscarriages	[48]
Cuello (2017); prospective	35 MS women and 40 pregnancies, vs 56 healthy women	No differences in peripartum outcomes	[28]
Goldacre (2017); retrospective	98 women and 191 pregnancies vs controls	No differences in peripartum outcomes	[49]
Houtchens (2018); retrospective	2115 women vs 2115 non-MS women	Mild increased number of infections, preterm deliveries, anemia and coagulation disorders	[50]
Fong (2018); retrospective	1185 deliveries vs controls	No differences in peripartum outcomes	[51]
Mueller (2002); retrospective	198 MS women vs 1584 controls	Increased risk of anemia and rehospitalization	[52]
van der Kop (2011); retrospective	432 MS women vs 2975 controls	No differences in peripartum outcomes	[53]
Kelly (2009); retrospective	10,055 deliveries in MS women vs 18 million controls	No differences in peripartum outcomes	[54]
Alroughani (2019); retrospective	164 pregnancies vs controls	No differences in peripartum outcomes	[33]
Jalkanen (2020); prospective	61 women	No differences in peripartum outcomes	[57]
Balslev Andersen (2019); retrospective	5760 pregnancies in MS women vs 27,664 from general population	No differences in peripartum outcomes	[55]
MS: Multiple sclerosis.			

Table 4. Cohort studies reporting the number of relapses and person-years in multiple sclerosis women.

Cohort	Pregpregnancy period, 1 year or longer		Pregnancy, 9 months		Puerperium, 3 months or longer		Ref.
	Relapses	Person-years	Relapses	Person-years	Relapses	Person-years	
Ghezzi (1981)	301	947	34	89	91	30	[12]
Korn-Lubetzki (1984)	40	199	20	143	32	50	[13]
Frith (1988)	193	327	40	106	14	25	[14]
Nelson (1988)	25	191	19	143	54	95	[16]
Salemi (2004)	542	1001	25	73	18	294	[20]
Bernardi (1991)	254	393	5	49	26	33	[15]
Hughes (2014)	164	514	178	669	127	207	[24]
Jesus-Ribeiro (2017)	52	127	22	95	27	32	[29]
Confavreux (1998)	164	227	71	170	68	55	[19]
Lai (2018)	7	14	1	10	8	3.5	[30]
Sadovnick (1994)	39	69	22	52	26	34	[18]
MacDonald (2019)	117	292	140	876	93	292	[34]
Alroughani (2019)	17	164	25	130	NA	NA	[33]
Cuello (2017)	25	70	7	26	18	70	[28]
Airas (2010)	50	61	18	46	21	15	[21]
Roulet (1993)	143	280	25	37	19	12	[17]
Portaccio (2011)	121	302	27	226	166	302	[22]
Benoit (2016)	106	186	41	121	53	40	[27]
Fares (2016)	5	64	0	48	0	16	[26]
Bsteh (2018)	147	387	52	290	495	774	[32]
Total	2296	5815	772	3158	1378	2380	
NA: Not available.							

disability worsening. Only in two retrospective cohorts, and in one prospective totaling 1618 MS women followed-up, pregnancy was protective in comparison with controls or the same patients year before pregnancy [38,42,43]. In five out of seven prospective cohorts, disability did not change; in one cohort decreased [35] and in another cohort disability increased after pregnancy but the number of patients included were small [30]. Disability worsening was analyzed in two ways: survival time to reach an EDSS of 6 points, or the mean EDSS score comparison before and after pregnancy.

In relation with peripartum outcomes (see Table 3), although there is not enough evidence to conclude that MS pregnant women have similar rates of complications and fetal outcomes, more studies revealed no differences than those that did. In five retrospective studies totaling 6823 pregnancies, there is an increased risk of infections [34,50], preterm deliveries [34,50], low birth weight [46,47], anemia [50,52] and rehospitalization [52], compared with non-MS pregnant women, versus the rest of studies pointing to similar outcomes and that totaled 19,619 women [5,28,33,37,48,49,51,53–55,57].

The rate of miscarriages and stillbirths was given in some studies, with low or not-significant rates compared with non-MS women [19,28,29,48–50,52,65].

Discussion

In this systematic review, we can confirm the assumption that the relapse rate decreases in MS pregnant women, and that it increases in the 3-month puerperium period. These results were obtained with two different approaches of meta-analysis (differences in the mean relapse rate, and rate ratios). Pregnancy is not associated with disability worsening. With the cumulated evidence, the misconception of the negative effect of pregnancy in MS women has disappeared, and the number of pregnancies in these women has increased over time [49]. However, there are issues pending elucidation. One of them is the risk of reactivation of MS after withdrawal of DMT in pregnancy, especially when fingolimod or natalizumab is used before pregnancy [33,66]. Second, given that the risk of relapses increases in puerperium, early resumption of treatment might reduce the risk of relapse after delivery [24,32,66,67], but additional evidence is needed [68]. In a large cohort that extended follow-up to 9–12 month puerperium, the ARR did not return to prepregnancy level, despite 17% of patients were on self-injectable DMT during pregnancy [31]. The influence of DMT drugs has not been analyzed in this review, and the subject is being investigated through data of large cohorts and registries.

There is no clear reason for an increased risk of relapse in puerperium, but it has been related with the abrupt decrease in estrogen levels and cessation of the immunotolerant state in pregnancy [69].

Some studies concluded that breastfeeding may be protective against relapse and disability [19,70–72], but it is still controversial and deserves further research.

The main strength in our meta-analysis is the large number of patients included, and the narrow confidence interval of the mean change in the ARR. The agreement between prospective and retrospective studies gives also robustness to the conclusions. In the sensitivity analysis both methods of meta-analysis (mean changes and SD in the ARR, and rate ratios according to the number of relapses for person-years) agreed in the results but also in heterogeneity. A limitation of this review is the inconsistency found among the different studies with regard to the size of ARR reduction, but not to the fact that pregnancy is associated with a reduced ARR. We tried to minimize heterogeneity by excluding studies with few cases or with largest SDs. Given that the demographic characteristics of patients are not different among cohorts analyzed, interaction by country or ethnic factors may explain the variation in the effect size found in our meta-analysis. In a recent meta-analysis focused on factors associated with relapses in MS patients, the authors found similar results pooled from four studies, with pregnancy being protective of relapses. The risk of relapses increased in puerperium according to the analysis from eight cohorts [73].

In terms of disability progression, pregnancy is too short to draw conclusions. It is worth mentioning a cohort study in which the patients with at least two pregnancies had lower risk of disability worsening [42]. However, this was not found in two cohorts of MS women with at least two pregnancies [27,40].

Conclusion

In conclusion, pregnancy in MS is associated with decreased ARR, but with increased ARR in puerperium, without influence on disability worsening. MS is not associated with poorer peripartum outcomes in comparison with non-MS women. *In vitro* fertilization increases the risk of relapse.

Summary points

- Pregnancy is associated with significant reduction of the relapse rate in women with multiple sclerosis. However, in the 3-month postpartum period the disease activity tends to rebound.
- After pregnancy there is no neurological disability worsening compared with the 1-year prepregnancy period.
- Successive pregnancies do not increase disease activity either.
- Pregnancy is not associated with worse peripartum outcomes and obstetrical complications in comparison with women of the general population.
- Breastfeeding *per se* does not increase the risk of relapses. However, it may be discouraged in women under determined disease modifying therapies.
- Assisted reproductive techniques in women with multiple sclerosis may result in relapse recurrence.

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