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# Assessing the Risk of Relapse After In Vitro Fertilization in Women With Multiple Sclerosis

Marie Mainguy,<sup>1</sup> Romain Casey,<sup>2,3,4,5</sup> Sandra Vukusic,<sup>2,3,4,5</sup> Christine Lebrun-Frenay,<sup>6</sup> Eric Berger,<sup>7</sup> Anne Kerbrat,<sup>8</sup> Abdullatif Al Khedr,<sup>9</sup> Bertrand Bourre,<sup>10</sup> Jonathan Ciron,<sup>11</sup> Pierre Clavelou,<sup>12</sup> Jerome De Seze,<sup>13</sup> Gilles Defer,<sup>14</sup> Ines Doghri,<sup>15</sup> Amélie Dos Santos,<sup>16</sup> Karolina Hankiewicz,<sup>17</sup> Pierre M. Labauge,<sup>18</sup> Emmanuelle Le Page,<sup>19</sup> Laurent Magy,<sup>20</sup> Elisabeth Maillart,<sup>21,22</sup> Eric Manchon,<sup>23</sup> Laure Michel,<sup>19</sup> Thibault Moreau,<sup>24</sup> Solène Moulin,<sup>25</sup> Jean Pelletier,<sup>26</sup> Corinne Pottier,<sup>27</sup> Aurélie Ruet,<sup>28,29</sup> Mariana Sarov,<sup>30</sup> Bruno Stankoff,<sup>31</sup> Eric Thouvenot,<sup>32</sup> Abir Wahab,<sup>33</sup> Helene Zephir,<sup>34</sup> Emmanuelle Leray,<sup>1,\*</sup> and David Axel Laplaud<sup>35,\*</sup>

## Correspondence

Dr. Leray  
emmanuelle.leray@ehesp.fr

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## Abstract

### Background and Objectives

Older studies reported an increased risk of relapse after in vitro fertilization (IVF) in women with multiple sclerosis (MS), which has not been confirmed by more recent works. All these studies had several limitations, such as small sample sizes, absence of a control population, or lack of neurologic validation of the relapses. The aim of this study was to determine the risk of relapse after IVF in women with MS.

### Methods

This retrospective cohort study included all women with MS who underwent IVF between 2009 and 2019 and a control group of women with MS who did not undergo IVF matched on age, MS duration, number of relapses, and MS-specific treatments in the previous year. Data on MS (disease duration, treatments, and relapses) were from the French MS Registry (OFSEP), whereas data on IVF (number of procedures, stimulation protocol type, and outcomes) were from the French national health insurance database. For this, the 2 databases were linked by indirect matching.

### Results

In total, 115 women with MS underwent 199 IVF procedures (mean age at first IVF: 33.9 ± 4.0 years; 45.2% had ≥2 IVF procedures), and 175 IVFs (88.0%) could be matched to specific patients. The risk of relapse in the 3 months after index date was the same in both IVF group and control group (0.06 relapse per patient-year), as confirmed also by the before-after analysis in the IVF group (0.06 vs 0.08).

\*These authors contributed equally to this work as co-senior authors.

<sup>1</sup>EHESP, CNRS, Inserm, ARENES UMR 6051, RSMS U 1309, Univ Rennes; <sup>2</sup>Hospices Civils de Lyon, Hôpital Neurologique Pierre Wertheimer, Service de Neurologie, sclérose en plaques, pathologies de la myéline et neuro-inflammation, Bron; <sup>3</sup>Centre de Recherche en Neurosciences de Lyon, Observatoire Français de la Sclérose en Plaques, INSERM 1028 et CNRS UMR 5292; <sup>4</sup>Université de Lyon, Université Claude Bernard Lyon 1; <sup>5</sup>Eugène Devic EDMUS Foundation Against multiple sclerosis, state-approved Foundation, Bron; <sup>6</sup>Neurology, UR2CA, URRIS, Centre Hospitalier Universitaire Pasteur2, Université Nice Côte d'Azur; <sup>7</sup>Department of Neurology, CHU de Besançon; <sup>8</sup>Neurology Department, CRC-SEP Rennes, Rennes Clinical Investigation Center CIC 1414, Rennes University Hospital Rennes University INSERM, CHU Ponchailou, University; <sup>9</sup>Department of Neurology, CHU d'Amiens; <sup>10</sup>Département of Neurology, CHU de Rouen; <sup>11</sup>Department of Neurology, CHU de Toulouse, CRC-SEP, F-31059 Toulouse Cedex 9, INSERM UMR1291 - CNRS UMR5051, F-31024 Toulouse Cedex 3, Université Toulouse III, Infinity; <sup>12</sup>Department of Neurology, CHU Clermont-Ferrand, F-63000 Clermont-Ferrand, Inserm, Neuro-Dol, F-63000 Clermont-Ferrand, Université Clermont Auvergne; <sup>13</sup>Department of Neurology and Clinical Investigation Center, CHU de Strasbourg, CIC 1434, INSERM 1434, F-67000; <sup>14</sup>Department of Neurology, CHU de Caen, MS Expert Centre, Avenue de la Côte-de-Nacre, Normandy University; <sup>15</sup>CRC SEP and Department of Neurology CHU de Tours, Hôpital Bretonneau; <sup>16</sup>Neurology, CHU de Poitiers, Hôpital Jean Bernard; <sup>17</sup>Department of neurology, Hôpital Pierre Delafontaine, Centre Hospitalier de Saint-Denis; <sup>18</sup>MS Unit, CHU de Montpellier, F-34295 Montpellier Cedex 5, University of Montpellier (MUSE); <sup>19</sup>Neurology Department CRCSEP, Rennes Clinical Investigation Center CIC-P 1414, Rennes University Hospital Rennes University INSERM; <sup>20</sup>Department of Neurology, CHU de Limoges, Hôpital Dupuytren, France; <sup>21</sup>Département de neurologie, Hôpital Pitié-Salpêtrière, APHP, Paris; <sup>22</sup>Centre de Ressources et de Compétences SEP Paris; <sup>23</sup>Department of Neurology, CH de Gonesse; <sup>24</sup>Department of Neurology, CHU de Dijon, EA4184; <sup>25</sup>Department of Neurology, CHU de Reims, CRC-SEP; <sup>26</sup>APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques, Service de Neurologie, Aix Marseille Univ; <sup>27</sup>Department of Neurology, Hôpital NOVO, site Pontoise; <sup>28</sup>Department of Neurology, University Hospital of Bordeaux; <sup>29</sup>Neurocentre Magendie, INSERM U1215, Bordeaux University; <sup>30</sup>Department of Neurology, CHU Bicêtre, Le Kremlin Bicêtre; <sup>31</sup>Department of Neurology, Paris Brain Institute, ICM, Inserm, CNRS, Hôpital de la Pitié Salpêtrière AP-HP, Sorbonne Universités; <sup>32</sup>Department of Neurology, Nimes University Hospital, F-30029 Nimes Cedex 9, IGF, CNRS, INSERM Montpellier Cedex 5, University of Montpellier; <sup>33</sup>Department of Neurology, APHP, Hôpital Henri Mondor, Créteil; <sup>34</sup>CHU Lille, CRCSEP Lille, Univ Lille, U1172, France; and <sup>35</sup>Service de Neurologie, Centre Hospitalier Universitaire (CHU) Nantes, Institut National de la Santé et de la Recherche Médicale (INSERM), Centre d'Investigation Clinique (CIC), Center for Research in Transplantation, Nantes Université.

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# Glossary

**ARR** = annualized relapse rate; **ART** = assisted reproductive technology; **CNIL** = Commission Nationale Informatique et Libertés; **DMT** = disease-modifying therapy; **GnRH** = gonadotrophin-releasing hormone; **IVF** = in vitro fertilization; **MS** = multiple sclerosis; **OFSEP** = Observatoire Français de la Sclérose En Plaques; **SNDS** = Système National des Données de Santé.

## Discussion

This study, using a 10-year clinical and administrative dataset, did not find any increased risk of relapse after IVF. The maintenance of disease-modifying therapies until IVF was a determining factor in reducing the risk of relapse.

## Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the CNS that primarily affects women and usually starts in young adulthood.<sup>1</sup> MS-specific disease-modifying therapies (DMT's) play a crucial role in reducing the risk of relapse and slowing disability progression.<sup>2,3</sup> Moreover, pregnancy decreases relapse occurrence, especially in the second and third trimesters.<sup>4,5,6</sup>

Assisted reproductive technologies (ART), such as in vitro fertilization (IVF), are medical procedures used primarily to address infertility.<sup>7</sup> IVF procedures generally begin with ovarian stimulation, using gonadotrophin-releasing hormone (GnRH) analogs that may be agonists or antagonists.<sup>8,9</sup> To increase the chances of success, several embryo transfers can be performed after the same IVF cycle ( $\geq 1$  frozen embryos after the initial fresh transfer).

Few studies investigated the risk of MS relapse after IVF. The first ones<sup>10-14</sup> (between 2006 and 2012) showed an increase in the annualized relapse rate (ARR) after IVF. In 2019, an American study<sup>15</sup> reported a nonsignificant difference in ARR after ART compared with control periods in 12 women with MS who underwent 22 ART cycles. All these studies had several limitations, especially small sample sizes ( $N = 6$  to 32), risk of recruitment bias, and lack of control population. Recently, 2 studies,<sup>16,17</sup> including one from our group, with larger sample sizes ( $N = 65$  and 225 women with MS, respectively) did not find any increased risk of relapse after IVF. All these studies<sup>10-17</sup> used a before/after intra-group comparison.

Therefore, the main objective of this study was to investigate the risk of relapse after IVF in women with MS, overall and according to the stimulation protocol (GnRH agonists and antagonists), using data from the French MS Registry (Observatoire Français de la Sclérose En Plaques; OFSEP) linked to the French national health insurance database (Système National des Données de Santé; SNDS). To strengthen the evidence robustness, we included also a matched control group of women with MS who never had IVF.

## Methods

### Study Design and Study Population

In this retrospective cohort study, we compared women with MS who underwent IVF and a control group of women with MS who did not undergo IVF.

We identified all women of childbearing age (15–49 years) with MS present in the OFSEP database from January 1, 2009, to December 31, 2019. We included in the IVF group only women who underwent IVF followed by at least 1 embryo transfer during the study period.

### Data Source

OFSEP is the national registry that collects clinical data on patients with MS followed at expert centers in France<sup>18</sup> (~69,000 patients in December 2020). Clinical and imaging data are retrospectively collected at the time of the first visit and then prospectively at the routine follow-up visits, usually once per year, using the dedicated European Database for Multiple Sclerosis software.<sup>19</sup>

The SNDS database<sup>20</sup> covers 98% of the French population regardless of age or socioeconomic status. It prospectively collects exhaustive anonymous individual data on the reimbursement of ambulatory activities (e.g., consultations and drug prescriptions) and hospital activities (all public and private hospitals). Each individual has a unique lifelong identifier, and the database includes the following information: sex, year of birth, insurance scheme (general scheme and specific insurance schemes for agricultural workers, self-employed people, and others), and long-term disease status (which allows 100% reimbursement), coded using the *International Classification of Diseases, 10th Revision* (ICD-10) codes and the corresponding starting year, if applicable.

As the 2 databases do not use the same unique identifier, we linked the OFSEP and SNDS databases by indirect matching, i.e., by combining several patient variables (such as sex, date of birth, date of death, department of residence, hospitalizations, treatments, and consultations) to create a unique key that allowed joining the databases. This procedure allowed matching 42,603 of the 52,034 eligible patients in the OFSEP database (matching rate = 81.9%), including 23,056 women.

Clinical data from the OFSEP database provided precise information on MS (e.g., date of MS onset and relapses, and DMT use), and administrative data from the SNDS gave access to non-MS data (e.g., IVF, stimulation protocols, and pregnancies).

### IVF and Ovarian Stimulation Protocols

In the SNDS database, we considered the following procedures: embryo transfer (codes: JSEC001 and JSED001), ovulation induction (code: YYYY032), embryo warming (code: 0083), and embryo thawing (code: 0063). We searched for both standard IVF (code: 0060) and intracytoplasmic sperm injection (code: 0061). The date of IVF corresponds to the date of fertilization. We excluded IVF procedures performed after October 1, 2019, because data on the 3-month post-IVF were not available. Over the study period, women could have had more than 1 IVF cycle with different outcomes (i.e., number of IVF procedures, transfers, and pregnancies).

Each IVF procedure included an initial stage of ovarian stimulation using GnRH agonists (nafarelin acetate and triptorelin) or antagonists (ganirelix and cetrorelix),<sup>21</sup> identified in the database using the drug claims.

### Control Group

We matched 1:1 women with MS who underwent IVF to women with MS not exposed to IVF based on age, MS duration, number of relapses in the previous year, and use of DMTs (no, moderately, or highly active) in the previous year. The index date was the IVF date of the matched IVF-exposed woman to obtain comparable follow-up periods. Matching on the number of relapses and DMT in the year before the index date was very strict, while matching on age and MS duration was more flexible, if needed. For women with several IVF procedures, we kept the same controls after checking that they remained matchable.

### Outcomes

The event of interest was relapse occurrence, defined as the appearance of new symptoms or reappearance or worsening of preexisting symptoms for at least 24 hours that occurred without fever at least 30 days after a previous relapse.<sup>22,23</sup> We extracted relapse information only from the OFSEP database because in this database, all relapses are validated by a neurologist (versus algorithm-based detection in the SNDS).

We considered 2 outcomes: the relapse rate in the 3-month post-IVF (ARR) (primary outcome) and the percentage of IVF procedures where the woman had at least 1 relapse in the following 3 months (secondary outcome). These outcomes were compared in the IVF group and control group and also within the IVF group (before-after IVF comparison in which each woman was her own control). Moreover, for the intragroup comparison, we also considered a control 3-month period 1 year before the IVF procedure because we hypothesized that these women may have been in a better disease

phase during the IVF procedure (i.e., a period with a lower risk of relapse). As some women did not have a 1-year follow-up period before IVF, the study population was smaller when considering this control period.

### Other Data

We considered that an IVF procedure was performed during DMT exposure (treated women thereafter) if the date of the IVF procedure was before the treatment end or within the period still under treatment effect (up to 3 months after the treatment end).

We considered an IVF procedure as successful if pregnancy was confirmed less than 14 days after embryo transfer, regardless of the pregnancy outcome. Outside this period, we considered that the pregnancy was spontaneous. We identified pregnancy through its outcome and calculated the start of pregnancy using a specific algorithm.<sup>24</sup> We considered birth as premature if the pregnancy lasted <37 weeks.

To evaluate temporal trends, we divided the study period into 2 subperiods: 2009–2014 and 2015–2019. This choice was based on DMT availability and on the types of stimulation protocols.

### Statistical Analyses

We performed descriptive analyses using means  $\pm$  SD for quantitative variables and proportions for qualitative variables. We calculated the ARR by dividing the total number of relapses during the observed period by the sum of the follow-up time. We compared ARR between groups using a zero-inflated Poisson regression because of the low occurrence of relapses observed in the descriptive analysis. We added an offset on the follow-up time to obtain the ARR. IVF was the statistical unit of analysis. As a woman could have undergone several IVF procedures (repeated measures), we included a random effect on the woman. We calculated the relapse incidence rates, incidence rate ratios, and the corresponding CIs and summarized them in a forest plot.

We used a zero-inflated Poisson regression to compare the ARR after IVF in the IVF group and control group (intergroup comparisons), and to compare the 3-month periods before and after IVF (intragroup comparison) and the control 3-month period 1 year before IVF.

We used the McNemar test to compare the percentage of IVF procedures where a woman had at least 1 relapse in the 2 periods of interest (before/after), followed by a multivariate logistic regression model.

Finally, we investigated potential prognostic factors of relapse occurrence in the 3 months after IVF using a logistic regression model.

We adjusted all models for age at IVF and the presence/absence of DMT at IVF, as well as their level of efficacy,

categorized as medium or high. We performed subgroup analyses based on the stimulation protocol (GnRH agonists vs antagonists), IVF outcome (success vs failure), and treatment status at the time of IVF (treated vs untreated). We replicated all analyses for both subperiods.

We considered results significant when  $p < 0.05$  and performed all analyses with R (v.4.2.2).

## Standard Protocol Approvals, Registrations, and Patient Consents

Ethical and data access approvals for the study were obtained according to the current French legislation.

Patients gave their informed consent to store their data in the OFSEP database and to use them for research in France and abroad.<sup>26</sup> The OFSEP-SNDS linkage was approved by the French data protection authority (Commission Nationale Informatique et Libertés CNIL; approval DR-2021-034 obtained on February 4, 2021) and was performed using medical records of patients who consented. Data were stored on a secure server at Eskemm Numérique (Rennes, France) that guarantees all the security requirements.

## Data Availability

According to data protection and the French regulation, the authors cannot publicly release the data from the French national health data system (SNDS). However, a request for data reuse may be made and would require prior approval from the French regulatory authorities.<sup>26</sup>

## Results

### Study Population

Between 2009 and 2019, among the 23,056 eligible women with MS, 175 women had at least 1 IVF. After excluding those who did not have at least 1 embryo transfer or had an IVF procedure after October 1, 2019, our study population included 115 women with MS who underwent a total of 199 IVF procedures during the study period (eFigure 1). Hundred-seven IVF procedures (53.8%) were performed with a GnRH antagonist and 80 (40.2%) with a GnRH agonist ( $n = 12$ , 6.0%, unknown protocol) (Table 1). Overall, 59 pregnancies (10 spontaneous and 49 IVF pregnancies) occurred in 54 different women (i.e., pregnancy rate of 29.6%). The IVF success rate was 24.6% (23.8% and 24.3% with an agonist and antagonist stimulation protocol, respectively). Regarding outcomes, 47 pregnancies (79.7%) resulted in live births (eTable 1). Moreover, 61 IVF procedures (30.7%) were performed in women taking DMTs or still under DMT effect ( $n = 57$  moderate-efficacy and  $n = 4$  high-efficacy treatments) (Table 1).

### IVF Group vs Control Group Comparisons

#### Characteristics of the Study Population and Control Group

Overall, 115 women and 175/199 IVFs (88.0%) could be matched. The remaining 24 IVFs were not matched because

the selected control no longer met the criteria for subsequent IVFs. As expected, the matching variables were similar in the control group ( $n = 115$ ) and IVF group (Table 2). However, the Expanded Disability Status Scale score at the index date was higher in the control group than the IVF group ( $2.1 \pm 2.1$  vs  $1.3 \pm 1.5$ ) and the relapse rate in the previous year was also higher (8.0% vs 5.1%).

### Intergroup Analysis

The ARR in the 3 months following index date was similar in the IVF group and the control group (0.06 vs 0.06) (Figure 1), whatever the stimulation protocol. The relapse rate after the index date was similar when comparing treated women in the IVF group (0.04) with those in the control group (0.04). Among untreated women, the relapse rate was also comparable between the IVF group (0.07) and the control group (0.08). Given the higher pregnancy rate in the IVF group, due to IVF and ovarian stimulation, we conducted a subanalysis on nonpregnant women only, confirming similar results with a nonsignificant  $p$  value of 0.857 and an ARR of 0.07 in the IVF group vs 0.08 in the control group.

In the 3 months following index date, 12 women in the IVF group (6.9%) and 10 women (5.7%) in the control group experienced at least 1 relapse ( $p = 0.8$ ). The multivariate logistic regression analysis also did not find any significant difference ( $p = 0.6$ ) in the percentages of women experiencing a relapse between groups, in agreement with the ARR data.

### Intragroup Comparison: Before vs After IVF

The ARRs in the 3 months after and before IVF were not significantly different (0.08 relapse per patient-year vs 0.06, respectively), overall and in the different subgroups (stimulation protocol and IVF outcome). Moreover, relapse rates before and after IVF were comparable, although they appeared slightly lower in treated women (0.05 before vs 0.07 after) than in untreated women (0.06 before vs 0.08 after). We found the same findings for the 3-month control period 1 year before IVF. We confirmed the pregnancy protective effect: in the IVF success subgroup, the ARR decreased from 0.05 to 0.02 in the main analysis and from 0.09 to 0.02 in the control period.

Regarding the secondary outcome, among the 199 IVF, 14 (7.0%) and 17 (8.5%) were performed in women who had at least 1 relapse in the 3 months before and after IVF ( $p = 0.7$ ), respectively. The multivariate logistic regression did not show any difference ( $p = 0.5$ ) in the percentage of women with a relapse before vs after IVF, which was consistent with the ARR data.

### Factors Linked to Relapse in 3 Months After IVF

In our study population, at least 1 post-IVF relapse was recorded after 17 (8.5%) of the 199 IVF. In univariate analysis, relapses in the previous year ( $p < 0.010$ ), time between IVF and last MRI ( $p < 0.001$ ), and MS duration ( $p < 0.05$ ) were significantly associated with the risk of relapse (Table 3).

**Table 1** Characteristics of the Study Population (Women With MS Who Underwent IVF)

Patient characteristics (N = 115)	
<b>MS type (%)</b>	
Relapsing-remitting MS	113 (98.3)
Primary progressive MS	2 (1.7)
<b>Age at MS onset (%)</b>	
Mean ± SD	26.0 ± 5.4
Median (Q1–Q3)	26 (22–30)
14–19 y	14 (12.2)
20–24 y	32 (27.8)
25–29 y	37 (32.2)
30–34 y	25 (21.7)
≥35 y	7 (6.1)
<b>Age at first IVF (%)</b>	
Mean ± SD	33.9 ± 4.0
Median (Q1–Q3)	34 (31–37)
23–27 y	6 (5.2)
28–32 y	37 (32.2)
33–37 y	50 (43.5)
38–42 y	22 (19.1)
<b>MS duration at first IVF (%)</b>	
Mean ± SD	7.9 ± 4.9
Median (Q1–Q3)	7 (4–11)
<5 y	32 (27.8)
5–9 y	41 (35.7)
10–14 y	35 (30.4)
≥15 y	7 (6.1)
<b>Number of IVF procedures during the study period (%)</b>	
1	63 (54.8)
2	31 (26.9)
3	13 (11.3)
4	7 (6.1)
7	1 (0.9)
<b>EDSS score in the 12 mo before IVF (%)</b>	
0	31 (26.9)
1–1.5	23 (20.0)
2–2.5	8 (7.0)
3–6	13 (11.3)
Missing	40 (34.8)

Continued

**Table 1** Characteristics of the Study Population (Women With MS Who Underwent IVF) (continued)

IVF characteristics (N = 199)	
<b>Age at IVF (%)</b>	
Mean ± SD	34.4 ± 4.2
Median (Q1–Q3)	34 (32–37)
23–27 y	9 (4.6)
28–32 y	55 (27.6)
33–37 y	88 (44.2)
38–42 y	47 (23.6)
<b>Stimulation protocol (%)</b>	
GnRH agonists	80 (40.2)
GnRH antagonists	107 (53.8)
Missing	12 (6.0)
<b>IVF (%)</b>	
With DMT	54 (27.2)
Glatiramer acetate	27 (13.6)
Interferon β	19 (9.6)
Natalizumab	4 (2.0)
Azathioprine	2 (1.0)
Dimethyl fumarate	2 (1.0)
Still under treatment effect <sup>a</sup>	6 (3.0)
Interferon β	5 (2.5)
Azathioprine	1 (0.5)
With DMT and still under the effect of another treatment	1 (0.5)
With azathioprine and still under the effect of glatiramer acetate	1 (0.5)
Without DMT	138 (69.3)
<b>Current DMT or time of DMT withdrawal (%)</b>	
Treated at the time of IVF	55 (27.6)
Stopped within 3 mo before IVF	6 (3.0)
Stopped in the 3–6 mo before IVF	9 (4.6)
Stopped within 6–12 mo before IVF	10 (5.0)
Stopped more than 12 mo before IVF or not treated	119 (59.8)
<b>Number of relapses in the y before IVF (%)</b>	
0	144 (72.4)
1	49 (24.6)
2	6 (3.0)

Abbreviations: DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; IVF = in vitro fertilization; MS = multiple sclerosis.  
<sup>a</sup> Up to 3 months after the treatment end.

**Table 2** Characteristics of the Study Population and Control Group

	Study population	Control group
<b>Matching variables</b>		
<b>Age at the index date (%)</b>		
Mean ± SD	34.4 ± 4.1	34.0 ± 4.0
Median (Q1–Q3)	34 (32–37)	34 (32–37)
22–27 y	7 (4.0)	9 (5.1)
28–32 y	50 (28.6)	56 (32.0)
33–37 y	79 (45.1)	76 (43.5)
38–43 y	39 (22.3)	34 (19.4)
<b>MS duration at the index date (%)</b>		
Mean ± SD	7.7 ± 4.7	7.8 ± 4.8
Median (Q1–Q3)	7 (4–11)	7 (4–11)
<5 y	48 (27.4)	49 (28.0)
5–9 y	67 (38.3)	61 (34.9)
10–14 y	52 (29.7)	56 (32.0)
≥15 y	8 (4.6)	9 (5.1)
<b>Number of relapses in the y before the index date (%)</b>		
0	135 (77.2)	135 (77.2)
1	34 (19.4)	34 (19.4)
≥2	6 (3.4)	6 (3.4)
<b>DMT in the y before the index date (%)</b>		
None	112 (64.0)	112 (64.0)
At least 1 moderate efficacy treatment	59 (33.7)	59 (33.7)
At least 1 high efficacy treatment	4 (2.3)	4 (2.3)
<b>Other variables</b>		
<b>Number of relapses in the 3 mo before the index date (%)</b>		
0	166 (94.9)	161 (92.0)
1	9 (5.1)	13 (7.4)
2	0 (0.0)	1 (0.6)
<b>EDSS score at the index date (%)</b>		
Mean ± SD	1.3 ± 1.5	2.1 ± 2.1
Median (Q1–Q3)	1 (0–2)	2 (1–3)
0	47 (26.9)	30 (17.1)
1–1.5	36 (20.6)	34 (19.4)
2–2.5	10 (5.7)	32 (18.3)

Continued

**Table 2** Characteristics of the Study Population and Control Group (continued)

	Study population	Control group
3–10	22 (12.5)	35 (20.0)
Missing	60 (34.3)	44 (25.2)
<b>Time between index date and last MRI, y (%)</b>		
Mean ± SD	2.7 ± 2.9	2.2 ± 2.9
Median (Q1–Q3)	1.8 (0.9–3.3)	0.9 (0.4–2.8)
<1 y	39 (22.3)	77 (44.0)
1–3 y	56 (32.0)	38 (21.7)
3–5 y	21 (12.0)	13 (7.4)
>5 y	20 (11.4)	22 (12.6)
Missing	39 (22.3)	25 (14.3)
<b>MRI-worsening (%)</b>		
Unknown or missing	114 (65.1)	100 (57.1)
No	33 (18.9)	51 (29.1)
Yes	28 (16.0)	24 (13.7)
<b>MRI-new lesions (%)</b>		
Unknown or no or missing	169 (96.6)	173 (98.9)
Yes	6 (3.4)	2 (1.1)
<b>MRI-gadolinium-enhancing lesions (%)</b>		
Unknown or missing	54 (30.9)	41 (23.4)
Negative	79 (45.1)	108 (61.7)
Positive	42 (24.0)	26 (14.9)

Abbreviations: DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.

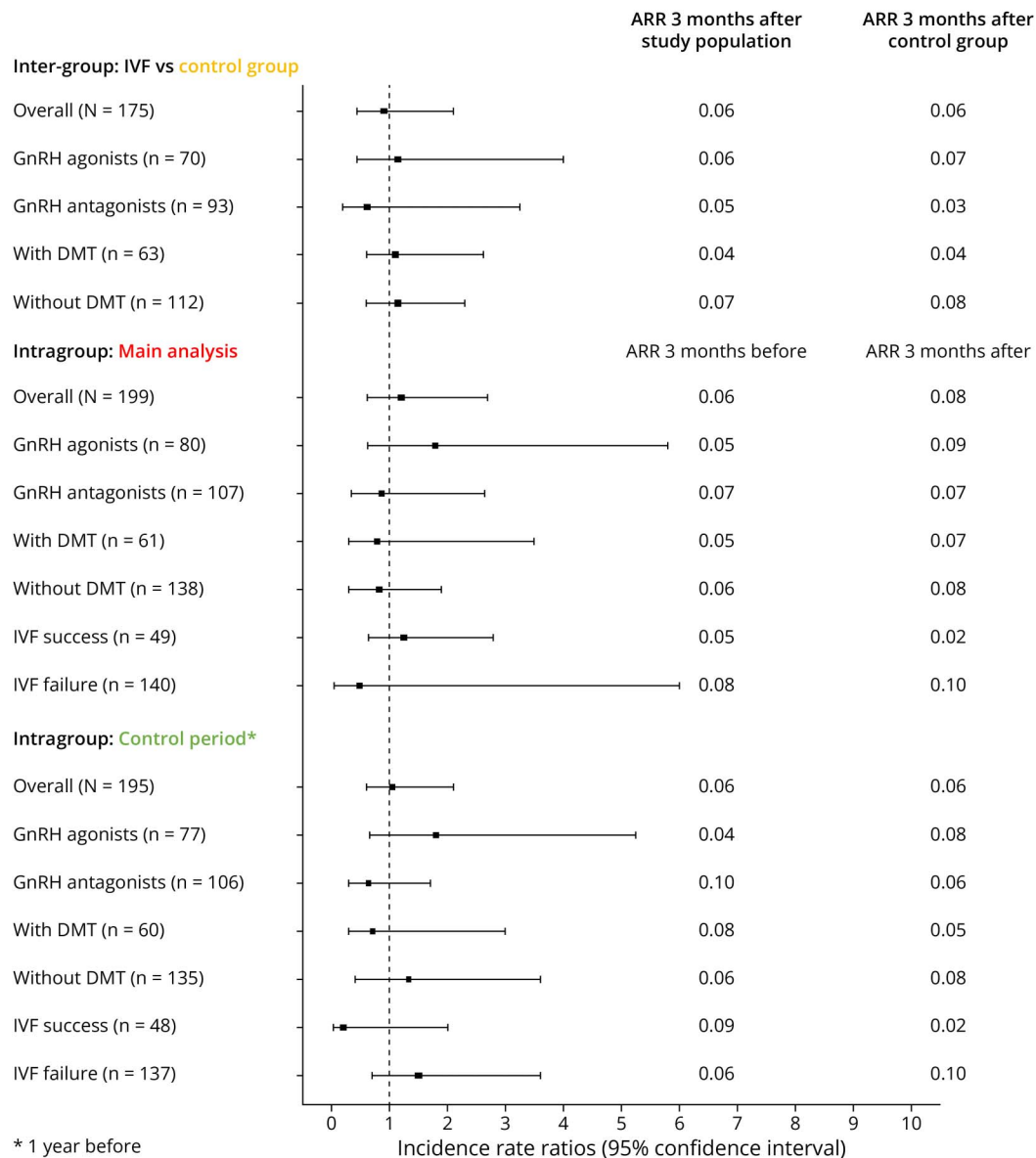
None of these associations remained significant in the multivariate analysis.

### Comparison of Subperiods: 2009–2014 vs 2015–2019

In the IVF group (n = 115), 76 women (66.1%) underwent at least 1 IVF procedure between 2009 and 2014 and 56 (48.7%) between 2015 and 2019. We included in both groups the 17 women (14.8%) who had IVF procedures in both subperiods.

Age at IVF was not different in the 2 subperiods (34.2 ± 3.9 years between 2009 and 2014 vs 34.6 ± 4.5 years between 2015 and 2019). However, MS duration at IVF was shorter in the 2015–2019 group (7.7 ± 4.1 years vs 8.3 ± 5.3 years). Moreover, women in this group were more often treated or still under treatment at IVF time (39.1% vs 25.0%). We

**Figure 1** Relapse Incidence Rates and Incidence Rate Ratios



observed several differences concerning treatments in the 2 subperiods (Table 4). Women who performed IVF between 2015 and 2019 started treatment at a younger age than those who performed IVF between 2009 and 2014 ( $28.7 \pm 6.4$  years vs  $32.5 \pm 6.7$  years). Similarly, they started treatment earlier in the disease course ( $2.6 \pm 3.2$  years vs  $6.1 \pm 6.2$  years). Accordingly, the part of disease duration under treatment was higher in the 2015–2019 period than in the 2009–2014 period (38.9% vs 24.4%). GnRH antagonists were more often used than GnRH agonists in the 2015–2019 period (65.5% vs 32.2%) (eFigure 2).

The risk of relapse after IVF was similar in the 2 subperiods (Figure 2, eTable 2). When we further divided women in the 2 subperiods (2009–2014 vs 2015–2019) in 2 subgroups (with/without treatment at IVF time) (Figure 3), we observed a decline in the ARR in all subgroups during pregnancy,

followed by a postpregnancy increase. This increase was less pronounced among women under treatment.

## Discussion

Using clinical and administrative dataset (through a linkage procedure) and intergroup (matched women with MS who underwent or not IVF) and intragroup (women with MS before and after IVF) analyses, we did not find any increased risk of relapse after IVF in women with MS in France, between 2009 and 2019, overall and in function of the stimulation protocol and IVF outcome.

Previous small-size studies<sup>10-14</sup> and recent larger studies<sup>15-17</sup> investigated the risk of relapse after IVF in women with MS with conflicting results. The 3 most recent studies<sup>15-17</sup> found no increased risk of relapse after IVF, as confirmed by this

**Table 3** Risk Factors of Relapse in the 3 Months After IVF

	Population with relapses (N = 17)	Population without relapses (N = 182)	p Value
<b>Age (%)</b>			
Mean ± SD	32.9 ± 4.5	33.8 ± 4.0	ns
Median (Q1–Q3)	34 (32–35)	34 (31–36)	
22–27 y	3 (17.6)	10 (5.5)	ns
28–32 y	2 (11.8)	59 (32.4)	
33–37 y	10 (58.8)	76 (41.8)	
38–42 y	2 (11.8)	37 (20.3)	
<b>MS duration (%)</b>			
Mean ± SD	4.8 ± 4.2	7.6 ± 4.8	<0.05
Median (Q1–Q3)	3 (2–6)	7.0 (4–11)	
<5 y	10 (58.8)	56 (30.8)	ns
5–9 y	3 (17.6)	62 (34.1)	
≥10 y	4 (23.6)	64 (35.1)	
<b>Number of relapses in the y before IVF (%)</b>			
0	9 (52.9)	141 (77.5)	<0.01
1	5 (29.5)	39 (21.4)	
≥2	3 (17.6)	2 (1.1)	
<b>Number of relapses in the 3 mo before IVF (%)</b>			
0	15 (88.2)	170 (93.4)	ns
1	2 (11.8)	12 (6.6)	
<b>DMT in the y before IVF (%)</b>			
None	14 (82.4)	118 (64.8)	ns
At least 1 moderate efficacy treatment	3 (17.6)	59 (32.4)	
At least 1 high efficacy treatment	0 (0.0%)	5 (2.8%)	
<b>EDSS score at first IVF (%)</b>			
0	2 (11.8)	46 (25.3)	ns
1–1.5	1 (5.9)	39 (21.4)	
2–2.5	0 (0.0)	10 (5.5)	
3–6	3 (17.6)	21 (11.5)	
Missing	11 (64.7)	66 (36.3)	
<b>Time between IVF and last MRI, y (%)</b>			
Mean ± SD	0.5 ± 0.3	2.9 ± 2.8	<0.001
Median (Q1–Q3)	0.5 (0.3–0.6)	1.9 (1.0–3.8)	
<1 y	5 (29.4)	21 (11.5)	ns

Continued

**Table 3** Risk Factors of Relapse in the 3 Months After IVF

(continued)

	Population with relapses (N = 17)	Population without relapses (N = 182)	p Value
1–3 y	1 (5.9)	37 (20.3)	
3–5 y	0 (0.0)	16 (8.8)	
>5 y	0 (0.0)	14 (7.7)	
Missing	11 (64.7)	94 (51.8)	
<b>MRI in the y before IVF-worsening (%)</b>			
Unknown or missing	14 (82.4)	122 (67.0)	ns
No	3 (17.6)	32 (17.6)	
Yes	0 (0.0)	28 (15.4)	
<b>MRI-new lesions (%)</b>			
Unknown or no or missing	17 (100.0)	176 (96.7)	ns
Yes	0 (0.0)	6 (3.3)	
<b>MRI-gadolinium-enhancing lesions (%)</b>			
Unknown or missing	6 (35.3)	57 (31.3)	ns
Negative	10 (58.8)	80 (44.0)	
Positive	1 (5.9)	45 (24.7)	

Abbreviations: DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; IVF = in vitro fertilization; MS = multiple sclerosis.

study. We think that the previously reported conflicting findings are due to differences in study populations and changes in MS management over time. Indeed, the earlier studies<sup>10–14</sup> included smaller samples (6–32 women who underwent between 10 and 78 IVF procedures). The women's mean age ranged from 29.8 to 32.0 years, and most of them received GnRH-agonist stimulation (60%,<sup>10</sup> 64.3%,<sup>11</sup> 42.3%,<sup>12</sup> 100%,<sup>13</sup> and 68.6%<sup>14</sup>). Women were not taking DMTs<sup>10,11,13</sup> or very few of them (6.4%<sup>12</sup> and 5.7%<sup>14</sup>). More recent studies<sup>15–17</sup> included larger samples (12–225 women and 22 to 338 IVF procedures) with older women (34.6–36.3 years) and less use of agonist stimulation protocols (31.8%,<sup>15</sup> 37.0%,<sup>16</sup> and 10.5%<sup>17</sup>). One study<sup>15</sup> included only untreated women at the time of IVF, and in the other 2, 24.3%<sup>16</sup> and 42.7%<sup>17</sup> of women were receiving DMTs at the time of IVF. We do not think that the changes in stimulation protocols over time explain the different results. Indeed, our subgroup analyses in function of the stimulation protocol did not highlight any difference. Regarding the use of DMTs, our analysis of the 2 subperiods (2009–2014 vs 2015–2019) did not find any significant difference. Nevertheless, we could hypothesize that better MS management in recent times, before the IVF procedure and from the disease onset, might contribute to the overall reduction of relapse occurrence.

**Table 4** Characteristics of the IVF Procedures Performed in 2009–2014 and 2015–2019

	IVF between 2009 and 2014	IVF between 2015 and 2019
<b>Patient characteristics (N = 132 including 17 in both periods) (%)</b>	76	56
<b>Age at MS onset</b>		
Mean ± SD	25.9 ± 5.2	26.6 ± 5.7
Median (Q1–Q3)	26 (22–30)	26 (23–31)
<20 y	8 (10.5)	7 (12.5)
20–24 y	24 (31.6)	12 (21.4)
25–29 y	24 (31.6)	19 (34.0)
30–34 y	16 (21.1)	13 (23.2)
≥35 y	4 (5.3)	5 (8.9)
<b>Age at first DMT</b>		
Mean ± SD	32.5 ± 6.7	28.7 ± 6.4
Median (Q1–Q3)	32.5 (27–38)	29 (24–34)
<25 y	7 (9.2)	12 (21.4)
25–30 y	19 (25.0)	12 (21.4)
30–35 y	11 (14.5)	11 (19.6)
35–40 y	17 (22.4)	9 (16.1)
>40 y	12 (15.7)	1 (1.9)
No DMT	10 (13.2)	11 (19.6)
<b>MS duration at first DMT</b>		
Mean ± SD	6.1 ± 6.2	2.6 ± 3.2
Median (Q1–Q3)	3.8 (0.9–9.8)	0.9 (0.5–3.8)
<1 y	18 (23.7)	24 (42.9)
1–3 y	10 (13.2)	6 (10.7)
3–5 y	6 (7.9)	7 (12.5)
5–10 y	15 (19.7)	6 (10.7)
>10 y	17 (22.3)	2 (3.6)
No DMT	10 (13.2)	11 (19.6)
<b>IVF characteristics (N = 199) (%)</b>	112	87
<b>Age at IVF</b>		
Mean ± SD	34.2 ± 3.9	34.6 ± 4.5
Median (Q1–Q3)	34 (31–37)	35 (32–38)
<30 y	13 (11.6)	14 (16.1)
30–35 y	45 (40.2)	28 (32.2)
35–40 y	42 (37.5)	33 (37.9)
>40 y	12 (10.7)	12 (13.8)
<b>MS duration at IVF</b>		
Mean ± SD	8.3 ± 5.3	7.7 ± 4.1
Median (Q1–Q3)	7.5 (4–11)	7 (5–10)

Continued

**Table 4** Characteristics of the IVF Procedures Performed in 2009–2014 and 2015–2019 (continued)

	IVF between 2009 and 2014	IVF between 2015 and 2019
<5 y	30 (26.8)	19 (21.8)
5–9 y	36 (32.1)	40 (46.0)
10–14 y	36 (32.1)	24 (27.6)
≥15 y	10 (9.0)	4 (4.6)
<b>Stimulation protocol</b>		
GnRH agonists	52 (46.4)	28 (32.2)
GnRH antagonists	50 (44.7)	57 (65.5)
Missing	10 (8.9)	2 (2.3)
<b>DMT during IVF or still under treatment effect<sup>a</sup></b>		
None	84 (75.0)	53 (60.9)
At least 1 moderate efficacy treatment	28 (25.0)	30 (34.5)
Glatiramer acetate	14 (12.5)	14 (16.1)
Interferon β	13 (11.6)	11 (12.6)
Azathioprine	1 (0.9)	3 (3.5)
Dimethyl fumarate	0 (0.0)	2 (2.3)
At least 1 high efficacy treatment	0 (0.0)	4 (4.6)
Natalizumab	0 (0.0)	4 (4.6)
<b>Proportion of treated disease duration until IVF</b>		
Mean ± SD	24.4 ± 33.5	38.9 ± 35.2
Median (Q1–Q3)	0 (0.0–57.0)	35.8 (0.0–74.4)
None	57 (50.9)	25 (28.8)
0–25%	20 (17.9)	13 (14.9)
25–50%	3 (2.6)	16 (18.4)
50–75%	17 (15.2)	12 (13.8)
75–100%	15 (13.4)	21 (24.1)

Abbreviations: DMT = disease-modifying therapy; GnRH = gonadotrophin-releasing hormone; IVF = in vitro fertilization; MS = multiple sclerosis.

<sup>a</sup> Up to 3 months after the treatment end.

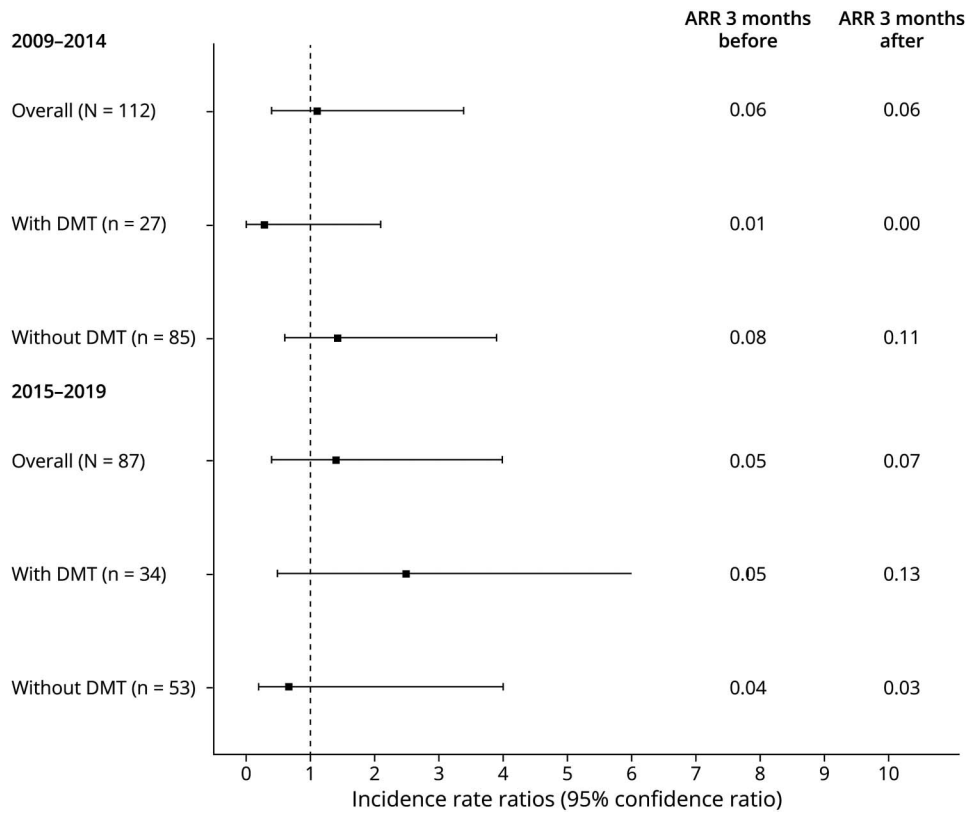
We could not identify any prognostic factor of relapse occurrence in the 3 months after IVF. The univariate analysis found significant associations with the number of relapses in the year before IVF and with MS duration, but they were not confirmed by the multivariate analysis. Nevertheless, we suggest to women, neurologists, and fertility specialists to plan IVF in a period when MS is stable and/or fully controlled with DMTs.

One strength of this study is the use of 2 linked databases. The clinical data from OFSEP provided accurate information on relapses and DMT, and the administrative data gave detailed information on IVF and pregnancies. The OFSEP database was an advance compared with our previous work on the topic<sup>16</sup> where we identified relapses in the SNDS database. In

the OFSEP database, a neurologist validated all relapses. Moreover, this database includes also relapses that did not require corticosteroid therapy. Nevertheless, the ARR were lower in this study (0.06 vs 0.08, before vs after IVF) than in the previous one<sup>16</sup> (0.20 vs 0.18). This could be due to differences in study population and MS management, but also because ARR seems to decrease over time in women before pregnancy and in the postpartum period.<sup>27</sup>

Comparison with a control group of women with MS who did not undergo IVF is another strength of this study. The fact that our previous results were confirmed by using an alternative design and a new data source makes us confident about the absence of increased risk of relapse after IVF. Moreover,

**Figure 2** Relapse Incidence Rates and Incidence Rate Ratios in Each Subperiod (2009–2014 vs 2015–2019)

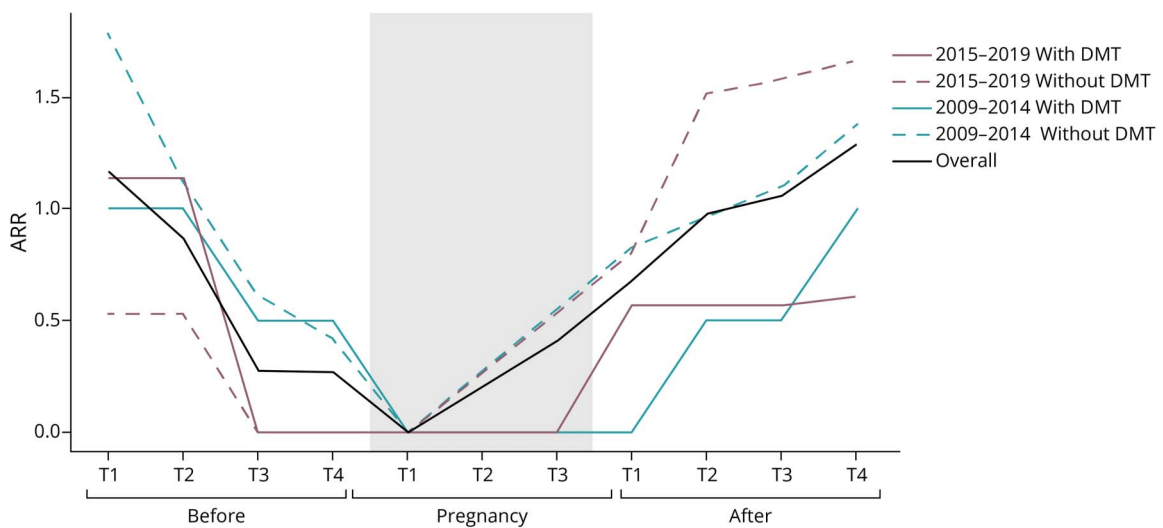


the same conclusion was reached in 2 previous American studies.<sup>15,17</sup>

The main limitation of this study is its retrospective nature, although most data were prospectively collected.<sup>28</sup> In

addition, the previous study<sup>16</sup> included 225 women with MS identified through the SNDS database who underwent IVF between 2010 and 2015. In this study, women were identified from the OFSEP registry, with IVF dates between 2009 and 2019, meaning there is a potential overlap between the 2

**Figure 3** ARR Values Before, During, and After Pregnancy in Each Subperiod



ARR = annualized relapse rate.

populations. Due to French legislative requirements, IDs differ between studies, making the reidentification of participants between different studies impossible. Overall, 124 of 199 IVF cases from this period may overlap with the previous study because they were performed over 2010–2015. Furthermore, the analysis of the 2015–2019 period (with only a brief overlap from January to September 2015) revealed comparable relapse rates before and after IVF, with no statistically significant difference, which confirms our findings are valid despite potential overlap with our previous work. Another limitation is that we did not match our control group by specific treatment but instead grouped treatments into 3 broad categories: no DMT, moderate efficacy DMTs, and high efficacy DMTs. This approach was necessary because matching by specific DMT would have led to the exclusion of more than half of the treated patients (42 of 63), which would have limited the representativeness of the control group.

To conclude, we think that it is essential to reassure women with MS about the absence of increased risk of relapse after IVF, whether performed with GnRH agonists or antagonists. Moreover, the IVF success rate (24.6%) was comparable with that of the general population (27.0%–34.5%).<sup>29</sup> Therapeutic advances in MS management might have contributed to a better disease control during the IVF time. Our results support the recent French and Spanish guidelines<sup>30,31</sup> that advise to plan infertility treatments in a period of stable disease and that promote good communication and strong coordination between neurologists and gynecologists/fertility specialists to ensure proper MS management and ART in the best conditions.

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## Author Contributions

M. Mainguy: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. R. Casey: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Vukusic: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C. Lebrun-Frenay: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. E. Berger:

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