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

Marie Mainguy (MSc)[1], Hélène Tillaut (MSc)[2], Adeline Degremont (PharmD, PhD)[3], Emmanuelle Le Page (MD)[4], Christelle Mainguy (MD)[5], Solène Duros (MD)[5], Elisabeth Polard (PharmD)[3], Emmanuelle Leray (PhD)[1]

[1] Unive Rennes, EHESP, CNRS, Inserm, ARENES-UMR, France

[2] Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail)-UMR, Rennes, France

[3] Pharmacovigilance, Pharmacoepidemiology and Drug Information Centre, Department of Clinical Pharmacology, Rennes University Hospital, Rennes, France

[4] Neurology Department CRCSEP, Rennes Clinical Investigation Centre CIC-P 1414, Rennes University Hospital Rennes University INSERM, Rennes, France

[5] Department of Gynecology Obstetric and Reproductive Medecine, University Hospital, Rennes, France

Corresponding author:
Emmanuelle Leray
emmanuelle.leray@ehesp.fr

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Abstract

Background and Objectives: Several studies have shown an increased risk of relapse after in vitro fertilization (IVF) in women with multiple sclerosis (MS), especially when a gonadotrophin-releasing hormone (GnRH) agonist stimulation protocol was used. Our objective was to investigate the risk of relapse after IVF in women with MS, overall and according to stimulation protocol (GnRH agonists vs antagonists), using data from the French national health insurance database.

Methods: This retrospective cohort study included all women with MS who have benefited from IVF between January 1, 2010, and December 31, 2015, in France. Three-month exposed periods after IVF were compared with unexposed periods before IVF, each woman being her own control. Four outcomes were considered: annualized relapse rate (ARR), proportion of IVF with relapse, difference in the number of relapses "after–before," and the delay from IVF to the first relapse. Relapses were identified by an algorithm based on MS-related hospital admissions and the use of corticosteroid therapy. Stimulation protocols and disease-modifying therapies (DMTs) were identified using drug claims. Zero-inflated Poisson regression models adjusted for age at IVF and the presence of DMT were used. A random effect on women was included because women may undergo multiple IVF procedures. Subgroup analyses by stimulation protocol and IVF outcome (pregnancy or failure) were conducted.

Results: A total of 225 women accounting for 338 IVF procedures were included (the mean age at the first IVF 34.6 ± 4.5 years; 36% of women underwent at least 2 IVF procedures during the period). No increase in the risk of relapse after IVF was found overall (before vs after IVF: 0.20 vs 0.18 relapse per patient-year; 7.7% vs 7.1% of IVF with women having at least one relapse) and in subgroups. A lower ARR before and after IVF was observed among women who remained treated until IVF.

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Discussion: The maintenance of DMT until IVF seemed to be a determining factor in reducing the risk of relapse. Women with MS should be reassured because we did not show an increased risk of relapse requiring the use of corticosteroid therapy after IVF neither with GnRH agonists nor with GnRH antagonists.

Introduction

Multiple sclerosis (MS) is a chronic, autoimmune disease of the central nervous system that particularly affects women and usually starts in young adulthood[1]. There is no cure, but MS-specific disease-modifying therapies (DMT) help to reduce risk of relapse and delay disability progression in patients with MS[2,3]. Pregnancy is also known to decrease relapse occurrence, especially in the second and third trimesters[4–6].

Assisted Reproduction Technology (ART) are medical procedures used primarily to address infertility, such as in vitro fertilization (IVF)[7]. IVF starts with ovarian stimulation, with Gonadotrophin-Releasing Hormone (GnRH) analogs, that can be either agonists or antagonists[8,9]. Several transfers can take place for the same IVF (one or more frozen embryo(s) + the first fresh transfer) to increase chance of success.

To date, only a few studies have considered the risk of MS relapses after IVF. All these studies[10–15] showed an increase in the annualized rate of relapses (ARR) after IVF compared to before, except the most recent one[15] which found for the first time a non-significant difference of ARR after IVF compared to before. Those studies had several limitations, especially small sample sizes and risks of selection bias.

The main objective of the present study was to investigate the risk of relapse after in vitro fertilization in women with multiple sclerosis, overall, and according to stimulation protocol

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(GnRH agonists vs GnRH antagonists), using data from the French national health insurance database.

Materials and methods

Study design and data source

This retrospective cohort study compared an "exposed" period of 3 months after IVF to an "unexposed" period of 3 months before IVF, each women being her own control. Moreover, we considered a control period of 3 months 1 year before IVF, as we hypothesize that patients may have been in a better phase of the disease at the time of IVF, i.e. a period with fewer relapses. Because some women did not have 1 year of follow-up before IVF, the study population was smaller when considering this control period.

The French national health insurance database[16] (Système National des Données de Santé; SNDS) covers 98% of the French general population without any age or wealth criteria. It compiles exhaustive anonymous individual prospective data regarding the reimbursement of ambulatory healthcare such as consultations and drugs prescriptions, as well as exhaustive hospital activity of all public and private hospitals.

Each individual is identified by a unique life-long identifier. The following characteristics are available: gender, year of birth, date of death, insurance scheme (general scheme, agricultural workers, self-employed and other schemes) and long term disease registration (LTD, which allows 100% reimbursement), coded according to ICD-10 codes[17] and its corresponding starting year, if applicable.

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Study population

Women of childbearing age (15 to 49 years) with MS were identified from January 1, 2010 to December 31, 2015 using a three-criteria algorithm: the presence of a long-term disease (LTD) status for MS, *or* MS-related hospital admissions (ICD-10 code G35), *or* reimbursement for MS-specific drugs (beta-interferon, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate and teriflunomide) [18–20]. Only data regarding patients with MS were accessed and stored in a secure environment. In the present study, only women who have benefited from IVF, followed by at least one embryo transfer during the study period (to get a chance of being successful) were included.

IVF and exposure to ovarian stimulation protocols

Women may experience different IVF history (one or several IVF, one or several transfer after IVF, one or several pregnancies, either related to IVF or spontaneous) over the study period. In the French health insurance database (SNDS), we identified procedures of interest among the procedures related to infertility[21] as follows: embryo transfers (coded "JSEC001" and "JSED001"), ovulation induction (coded "YYYY032"), embryo warming (coded "0083") and embryo thawing (coded "0063").We considered both standard IVF and IVF called IntraCytoplasmic Sperm Injection (ICSI) , coded "0060" and "0061" respectively. The date of IVF corresponds to the date of fertilization. IVF performed after October 1, 2015 were excluded as the post-IVF 3-month period was not available.

Each IVF procedure includes an initial stage of ovarian stimulation by GnRH agonists or antagonists, whose identification in the database was based on drugs claims. Nafarelin acetate and triptorelin were classified as GnRH agonists while ganirelix and cetrorelix were classified as GnRH antagonists[21].

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Relapses outcomes

The event of interest was the occurrence of relapse which is usually defined as new symptoms or worsening of pre-existing symptoms for at least 24 hours and occurring at least 30 days after a previous relapse[22,23]. As this clinical event was not directly available in the database, we used a recently published specific algorithm based on hospital admissions and/or use of corticosteroids (either oral or intravenous)[24–26].

Four outcomes were considered: the annualized relapse rate (ARR) and the proportion of IVF where the woman had at least one relapse after IVF were compared with before IVF; the difference in the number of relapses after vs. before IVF was also calculated, as well as the delay from IVF to the first relapse within one year.

Other data

Exposure to DMT was defined using dates and quantities of drug issued by pharmacists (deliveries made on a monthly basis). An IVF was considered as exposed if the date of IVF was prior to the end of treatment.

An IVF procedure was defined as successful when a pregnancy occurred less than 14 days after an embryo transfer. Outside this period, a pregnancy was considered as spontaneous. Pregnancy was identified through its issue, and start of pregnancy was calculated using a specific algorithm[27]. Pregnancies of less than 37 weeks were considered as premature.

Statistical analyses

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Descriptive analyses were performed using mean ± standard deviation for quantitative variables and proportions for qualitative variables. First, the annualized relapse rate (ARR) was defined as the sum of the number of relapses in the considered period divided by the sum of the follow-up times. To compare ARR between the 3-month period before IVF with the 3 following months, a zero-inflated Poisson regression (ZIP) was used (R-software packages lme4 and ggeffects). As the occurrence of relapses was not frequent (based upon descriptive analysis), i.e. the expected frequency of zero was high, a counting model with zero inflation was the most appropriate. As the data were not over dispersed, this model was preferred to a negative binomial model. An offset on the follow-up time was added to obtain the ARR. IVF was the statistical unit of analysis and as a woman can perform several IVF procedures (repeated measures), a random effect on the woman was included. Incidence rate ratios (IRR) and their confidence intervals (CI) were calculated and summarized in a forest plot.

Second, regarding the proportion of IVF where the woman had at least one relapse in the two periods of interest, a McNemar test was used to check whether it was the same women who experienced relapses before and after IVF. Then, a logistic regression was used (mclogit package) and a random effect on IVF was added to compare the two periods.

Third, the difference between the number of post-IVF relapses and the number of pre-IVF relapses was calculated, categorized in three ordered classes: decrease, no change, and increase, and modeled using an ordinal multinomial logistic regression.

Fourth, to measure time from IVF to first relapse within one year, a Kaplan Meier survival curve was estimated overall and according to subgroups of interest and compared with logrank tests (survminer package).

All models were adjusted for age at IVF and presence/absence of DMT at IVF.

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Subgroup analyses were performed according to the stimulation protocol (GnRH agonists *vs.* antagonists) and IVF outcome (success *vs.* failure).

Finally, two sensitivity analyses were conducted. First, a duration of 6 months was taken instead of 3 months as periods of interest before and after IVF. Second, an IVF was assumed as exposed if the patient had stopped treatment for less than 3 months (to consider a possible persistent effect of the treatment after its cessation). Results were considered significant when $p<0.05$. All analyses were conducted using R (v.3.6.0).

Standard Protocol Approvals, Registrations, Patient Consents

Ethical and data access approvals for the study were obtained in accordance with current French legislation (IDS approval decision n°191, May 25, 2016 and CNIL decision DE-2017-026, March 21, 2017).

Data Availability Statement

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 the obtention of prior approval of the French regulatory authorities (https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees).

Results

Study population

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Between 2010 and 2015, among the 46,294 women of reproductive age who had MS, 244 women had IVF with at least one embryo transfer. After excluding inconsistencies, our study population was composed of 225 patients who benefited from a total of 338 IVF procedures during the study period, with a systematic follow-up duration of 3 months before and after (Figure 1).

The mean age at first IVF was 34.6 ± 4.5 years and 36% of women had at least two IVF during the period (Table 1). In case of repeated IVF, the mean interval between two procedures was 267 ± 283 days (median 182 days). Regarding the stimulation protocols, 205 IVF (60.7%) were performed with a GnRH antagonists protocol and 125 (37.0%) with a GnRH agonists protocol, and the 8 remaining (2.3%) could not be determined (Table 1). Overall, 142 pregnancies (33 spontaneous and 109 IVF pregnancies) occurred in 121 different women, i.e. a pregnancy rate of 42.0% (Figure 1) over the study period. The IVF success rate was 32.2% (27.8% if agonists stimulation protocol *vs* 34.4% if antagonists protocol). Regarding outcomes, 108 pregnancies (76.1%) resulted in live births, of which 17 (15.7%) were premature (Table 2). When we focused on the period of interest of the 3 months following IVF, we observed 92 IVF pregnancies, i.e. 92 IVF successes, and 246 IVF failures (no IVF pregnancy within 3 months). However, we also observed 8 cases of spontaneous pregnancy among the IVF failures, that were excluded in the subgroup analysis according to IVF outcome. Finally, the subgroup analysis was performed on 92 IVF successes and 238 failures. Of the 338 IVF, one quarter (82, 24.3%) were performed among women under DMT (71 on first-line treatment and 11 on second-line treatment). Twelve women stopped DMT in the 3 months preceding IVF and 9 women in the 3 to 6 previous months (Table 1).

ARR before and after the IVF

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The ARR in the year before IVF was 0.35 relapses per patient-year. Among the 338 IVF, 314 (92.9%) did not result in any relapse, leading to an overall ARR of 0.18 in the three months after IVF, compared to 0.20 in the three months before IVF. As shown in Figure 2 and Table 3, there was no statistically significant increase in the ARR in the 3 months following IVF compared to the 3 months before, overall and in subgroups. The ARR was lower in treated patients (0.15 before IVF; 0.13 after) than in untreated patients (0.28 before IVF; 0.25 after). The protective effect of the pregnancy was also observed (the ARR decreased from 0.30 to 0.07). Among the 238 IVF failures, 181 women (76.1%) were not treated at the time of IVF, and only 6 (3.3%) women restarted treatment within 3 months of IVF.

We found the same findings when using the 3-month control period one year before IVF (0.13 before IVF; 0.09 after) (Figure 2 and Table 3). Only the "GnRH agonists and IVF failure" subgroup reached statistical significance but towards a decreased ARR after IVF, probably due to a high ARR before IVF (0.72).

As natalizumab and fingolimod are associated with a risk of rebound after stop, we checked how many women were in that case. Among the 4 women who stopped natalizumab in the 6 months before IVF, three of them (75.0%) had a relapse after stop, which occurred in the 3 months before IVF. In addition, two of the 4 women switched to interferon within one month, and then were considered as treated at the time of IVF, while the 2 other women remained untreated. Among the 2 women who stopped fingolimod treatment in the 6 months before IVF, none of them had a relapse. One woman switched to glatiramer acetate and one was untreated when she performed IVF.

The proportion of relapses

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Among the 338 IVF, 26 women (7.7%) had at least one relapse in the 3 months before and 24 women (7.1%) had at least one relapse in the 3 months after IVF (6 women had relapse both before and after IVF). The multivariate logistic regression did not show any difference in the proportions of women having relapse before *vs.* after IVF, which was consistent with the results from the zero-inflated Poisson regression.

Among the few women who had a relapse after IVF, only 2 were treated (2/82=2.4% *vs.* 22/256=8.6% among untreated women).

The same findings were found when using the 3-month control period one year before IVF (9.1% *vs.* 7.0% of women with at least one relapse, respectively before and after IVF).

The difference in the number of relapses after-before

The majority of IVF was associated with a stable number of relapses (88.8%), some had a decrease (5.9%) and others had an increase (5.3%). In this multivariate analysis where the reference class was “No change”, no significant association was found (Table 4). Only increasing age was associated with a lower risk of having an increased number of relapses after IVF.

In contrast, using the control period 1 year before IVF, women who had a GnRH antagonists protocol had a lower risk (OR<1) of having a decrease in their ARR after IVF than no change, compared to GnRH agonists.

Time to first relapse within one year of IVF

The Kaplan-Meier analyses did not reveal any significant difference in the time to first relapse in the year following IVF between the two stimulation protocols, despite a p-value near

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significance (p=0.052) (Figure 3). When restricting to the 3 first months after IVF, no significant difference (p=0.99) was found.

The two sensitivity analyses confirmed all these results regarding the four outcomes.

Discussion

In the present study, we did not find any significant increase in the risk of relapse requiring use of corticosteroids therapy after IVF compared to before IVF in women with MS in France, between 2010 and 2015, overall and according to the stimulation protocol and the outcome of IVF. These results differ from several previously published studies and do not support the hypothesis that GnRH agonists protocol are responsible for the ARR increase. Thus, our findings may have direct implications in the management of women with MS who are pursuing fertility treatment.

The ARR in the year prior to IVF was 0.35 relapses per patient-year, which was comparable to recent studies about pregnancy and MS[28,29], and probably reflects the current risk of relapse in the therapeutic area. Among studies that focused on the risk of relapse after IVF, it was comparable to those of Hellwig and al.[11] (0.29) in 2008 and Bove and al.[15] (0.27) in 2019, but lower than Correale and al[13] (0.42) in 2012 and Michel and al.[14] (0.80) in 2012. In the study from Laplaud et al.[10] no woman had a relapse in the 3 months before IVF. Treatment epoch may explain such differences. Indeed, the arrival of new DMT combined with a better knowledge of prognostic factors in MS have led to changes in practices from neurologists towards earlier treatment in the disease course. It also applies to pregnancy, where more and more women with MS keep their treatment until conception, or even during pregnancy for

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women with active disease[20]. Indeed, the proportion of women having DMT at the time of IVF was almost 25% in our study, while it was null in the previously published series. We do expect that use of DMT until IVF (mainly first-line treatments) helps preventing occurrence of relapse, as highlighted by the very low number of treated women having a relapse in the 3 months following IVF compared to untreated ones (2.4% vs 8.6%, respectively). Among the 24 women who had a relapse within three months prior to IVF, 3 of them have recently stopped natalizumab, and may experience a disease rebound. Due to the limited number of women who restarted DMT earlier after IVF failure (n=6), we cannot make a link between the absence of relapse and the immediate restart of DMT.

To identify MS relapses, we relied on a recent algorithm based on 5 criteria and which allowed identification of relapses requiring hospital admission or corticosteroids therapy. It means that "benign" relapses (i.e. not seen by neurologists or not needing use of corticosteroids therapy) were not considered in the outcomes, which may imply that ARR may be underestimated. However, in a study using this algorithm of identification of relapses[25], the annual relapse rate and the proportion of patients having at least one relapse were close to other studies using clinical data. Finally, because the present study was based on health insurance data, we can know when a MRI was performed, but we cannot access to MRI results to confirm relapses. Regarding treatment of relapses during pregnancy, there is no specific recommendation[30], but we cannot rule out that neurologists may use less corticosteroids therapy during pregnancy. Indeed, several studies (outside MS) highlighted an excess risk of cleft lip and palate with high-dose corticosteroid exposure in the first trimester of pregnancy[31–33], but this was not systematically observed[34–37]. If so, the risk of relapse after IVF may have been under-estimated in pregnant women. This limitation should not question our findings as the number of pregnant women was less than half, and above all, subgroup

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analyses offered the opportunity to consider separately IVF successes (i.e. pregnant women) and IVF failures.

In the present study, the date of identification of relapses corresponded to the date of care which necessarily occurred later than first symptoms. In the previously published studies, the relapses were identified by a neurologist, who was able to retrace the history and note the date of relapse onset. Such discrepancy means that we may have missed some relapses, which started at the third month after IVF, but were treated in the fourth month for example. Similarly, it was possible that post-IVF relapses in our analysis may have started before IVF and were therefore misclassified. After verification, only one woman had a relapse identified 14 days after IVF which could have started before the procedure. Finally, the values of ARR and the dynamics of the ARR around pregnancy (data not shown) led us think that the algorithm was rather efficient. It has also been recently shown that administrative databases detect less relapses on average than clinical databases[38] (mean ARR of 0.44 for clinical data, 0.53 for claims data and 0.62 for pregnancy-specific registry). To deal with this potential limitation regarding relapse ascertainment, we plan to replicate the present analysis on data from the French Observatory of Multiple Sclerosis (OFSEP)[39] linked to the French health insurance database. Such linkage will have the advantage of combining strengths of both data sources, and will also offer the opportunity to assess the properties of the relapse algorithm.

Regarding calendar period, use of IVF stimulation protocols in MS patients has also evolved over time, probably linked to previous studies showing an increased risk of relapse after GnRH agonists stimulation. Thus, the GnRH antagonists protocol was the most frequent in our study (60.7%) in contrast to the other studies. We did not find any increase in the ARR following IVF, whatever the protocol.

Moreover, in the previous studies, patient recruitment was based on neurologists, which may have favored the inclusion of more active patients whereas the French health insurance system

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used in the present study is almost exhaustive and free from any selection bias. Risk of recruitment bias combined with small sample sizes (6 to 32 patients and 10 to 78 IVF) may explain statistical significance of previous results.

Indeed, one strength of the present study is the number of patients included, 225 women and 338 IVF, as well as data source which is nation-wide and almost exhaustive (98% coverage). In addition, when comparing the spontaneous pregnancy rate (between 17% to 24%) in the general population who have benefited from IVF[40] to that of MS women in the present study (23.2%) we find comparable results. However, such French health insurance database has also limitations. For instance, for drugs (DMT and stimulation treatments), we have the date of delivery from the pharmacist and not the date of effective use, while dates of medical procedures such as IVF are exact. Therefore, there is a risk of overcounting exposed pregnancies. Also, the database did not provide the context of infertility.

From a methodological point of view, we tested different statistical models to ensure the robustness of the results. IVF was the unit of analysis and inclusion of a random effect was essential as women may undergo several IVF procedures. It also means that analyses needed to be adjusted for other characteristics such as age and presence of DMT. In addition, before-after design offers the opportunity to fully adjust for individual characteristics, including unmeasured confounding factors. Moreover, we compared the ARR at 3 months after IVF with a control period one year before IVF as IVF are expected to be scheduled outside an inflammatory period.

Despite several limitations, we do think that women with MS should be reassured about the absence of increased risk of relapse requiring use of corticosteroids therapy after IVF, whether performed with GnRH agonists or GnRH antagonists. Thus, there should be no hesitation to use IVF among women with MS who have difficulties conceiving. Moreover, the stimulation protocol should be adapted to the patient and to the context of infertility and not to

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MS, contrary to what may be done today. To conclude, we did not find any increase of the risk of MS relapse requiring hospitalization or use of corticosteroids therapy after IVF in a nation-wide exhaustive dataset over 6 years.

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Conflict of Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Table 1. Characteristics of the study population.

Patient characteristics (N = 225)	
Age at MS identification	
Mean ± SD	29.7 ± 5.6
Median [Q1-Q3]	30 [26-33]
Age at first IVF	
Mean ± SD	34.6 ± 4.5
Median [Q1-Q3]	35 [31-38]
Health insurance scheme	
General insurance scheme excluding CMU	188 (83.6%)
CMU beneficiaries	19 (8.4%)
Agricultural workers	6 (2.7%)
Self-employed workers	8 (3.6%)
Other	4 (1.7%)
Number of IVF during the period	
1	144 (64.0%)
2	56 (24.9%)
3	19 (8.5%)
4	5 (2.2%)
5	1 (0.4%)
IVF characteristics (N = 338)	
Protocol type	
GnRH agonists	125 (37.0%)
GnRH antagonists	205 (60.7%)
Missing	8 (2.3%)
IVF	
With DMT	82 (24.3%)
Without DMT	256 (75.7%)
DMT during IVF	
First-line treatment	71 (86.6%)
Glatiramer acetate	34 (41.5%)
Interferon beta	36 (43.9%)
Azathioprine	1 (1.2%)
Second-line treatment	11 (13.4%)
Fingolimod	1 (1.2%)
Natalizumab	10 (12.2%)
Current DMT or time to stop DMT	
Treated at time of IVF	82 (24.3%)
Stopped within 3 months prior to IVF	12 (3.6%)
Stopped in the 3 to 6 months prior to IVF	9 (2.6%)
Stopped within 6 to 12 months prior to IVF	22 (6.5%)
Stopped for more than 12 months or not treated	213 (63.0%)

Abbreviations: MS, Multiple Sclerosis*;* SD, Standard Deviation; Q1-Q3, quartiles 1-3; CMU (Couverture Maladie Universelle), universal health insurance*;* IVF, In Vitro Fertilization*;* DMT, Disease-Modifying Therapy.

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Table 2. Pregnancy outcomes and mean gestational age.

Pregnancy outcomes	**N= 142 (100%)**	**Gestational age (in weeks)**
Livebirth	108 (76.1%)	38.1 ± 3.4
Elective abortion	2 (1.4%)	10 / 13
Therapeutic abortion	3 (2.1%)	15 / 17 / 21
Spontaneous abortion	15 (10.6%)	
< 14 weeks	10	7.8 ± 2.1
> 14 weeks	5	34.2 ± 9.7
Molar pregnancy	5 (4.2%)	7.6 ± 3.2
Ectopic pregnancy	3 (2.1%)	4 / 6 / 8
Stillbirth	2 (1.4%)	22 / 26
Unknown outcome	4 (2.8%)	26 / 38 / 39 / 40

if N ≥ 5 then mean ± standard deviation

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Table 3. Annualized Relapse Rate and Incidence Rate Ratio 3 months after IVF compared to 3 months before, and then, to 3 months, one year before.

	ARR before	**ARR after**	**Incidence Rate Ratio [95% confidence interval]**
Main analysis (3 months before IVF)			
Overall (N=338)	0.20	0.18	0.91 [0.7 ; 2.0]
GnRH agonists (N=125)	0.17	0.17	0.99 [0.6 ; 4.0]
GnRH antagonists (N=205)	0.23	0.21	0.88 [0.6 ; 2.4]
IVF success (N=92)	0.30	0.07	0.25 [0.07 ; 1.2]
IVF failure (N=238)	0.20	0.21	1.08 [0.8 ; 2.5]
GnRH agonists + IVF success (N=38)	0.13	0.04	0.33 [0.06 ; 5.0]
GnRH antagonists + IVF success (N=53)	0.33	0.06	0.20 [0.04 ; 2.1]
GnRH agonists + IVF failure (N=83)	0.01	0.01	1.11 [0.6 ; 5.5]
GnRH antagonists + IVF failure (N=148)	0.23	0.24	1.06 [0.7 ; 3.9]
Control period (3 months one year before IVF)			
Overall (N=285)	0.13	0.09	0.72 [0.7 ; 1.2]
GnRH agonists (N=101)	0.49	0.20	0.40 [0.2 ; 1.1]
GnRH antagonists (N=177)	0.13	0.14	1.07 [0.7 ; 3.2]
IVF success (N=81)	0.13	0.09	0.67 [0.1 ; 5.6]
IVF failure (N=204)	0.27	0.20	0.73 [0.7 ; 1.5]
GnRH agonists + IVF success (N=33)	0.06	0.06	1.00 [0.08 ; 10.0]
GnRH antagonists + IVF success (N=48)	0.17	0.09	0.50 [0.07 ; 7.0]
GnRH agonists + IVF failure (N=69)	0.70	0.20	0.30 [0.1 ; 0.9]
GnRH antagonists + IVF failure (N=128)	0.14	0.16	1.12 [0.7 ; 4.3]

Abbreviations: IVF, In Vitro Fertilization; ARR, Annualized Relapse Rate.

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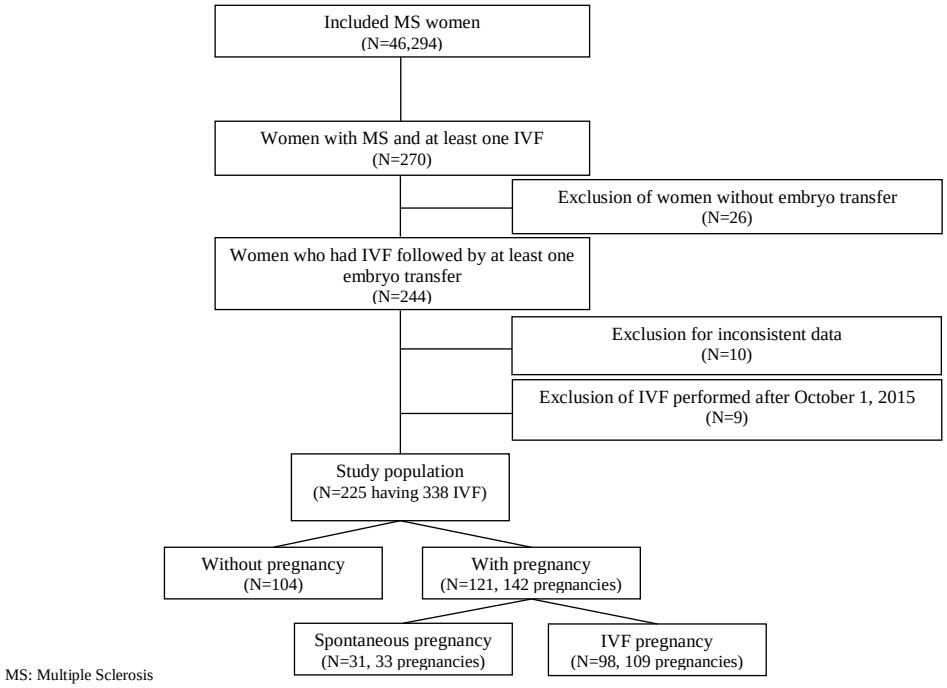
Table 4. Results of the ordinal multinomial regression over two control periods: main analysis and control period.

	Increase vs. No change		**Decrease vs. No change**	
	OR	**p-value**	**OR**	**p-value**
Main analysis (3 months before IVF)				
Intercept	5.08 [0.15 ; 172.72]	0.366	0.14 [0.003 ; 5.89]	0.305
Age at IVF	0.89 [0.80 ; 0.98]	**0.023**	0.97 [0.88 ; 1.08]	0.601
Presence of DMT at the time of IVF vs. No treatment	0.16 [0.02 ; 1.25]	0.081	0.69 [0.22 ; 2.12]	0.514
GnRH antagonists vs. GnRH agonists	1.35 [0.48 ; 3.79]	0.570	1.51 [0.56 ; 4.06]	0.417
Success vs. Failure of IVF	0.37 [0.10 ; 1.34]	0.130	1.15 [0.44 ; 3.02]	0.782
Control period (3 months one year before IVF)				
Intercept	1.56 [0.02 ; 133.92]	0.844	0.57 [0.01 ; 24.41]	0.769
Age at IVF	0.90 [0.79 ; 1.03]	0.122	0.96 [0.87 ; 1.07]	0.498
Presence of DMT at the time of IVF vs. No treatment	0.26 [0.03 ; 2.06]	0.200	0.78 [0.24 ; 2.52]	0.683
GnRH antagonists vs. GnRH agonists	1.54 [0.39 ; 6.07]	0.539	0.36 [0.13 ; 0.99]	**0.049**
Success vs. Failure of IVF	0.69 [0.17 ; 2.71]	0.592	0.37 [0.10 ; 1.37]	0.138

Abbreviations: OR, Odds Ratio; IVF, In Vitro Fertilization; DMT, Disease-Modifying Therapy.

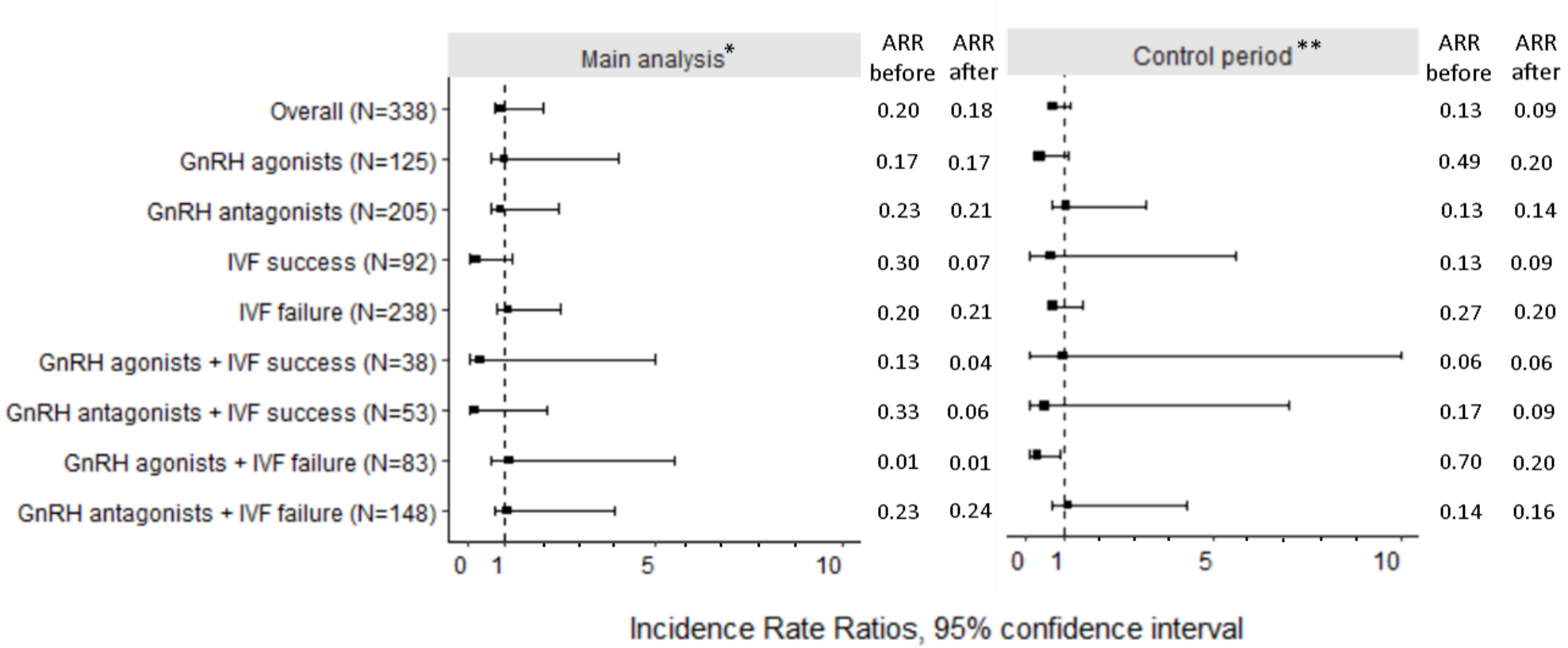
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Figure 1. Flow-chart of the study population (N=225) in women with MS in France from 2010 to 2015.



MS: Multiple Sclerosis
IVF: In Vitro Fertilization

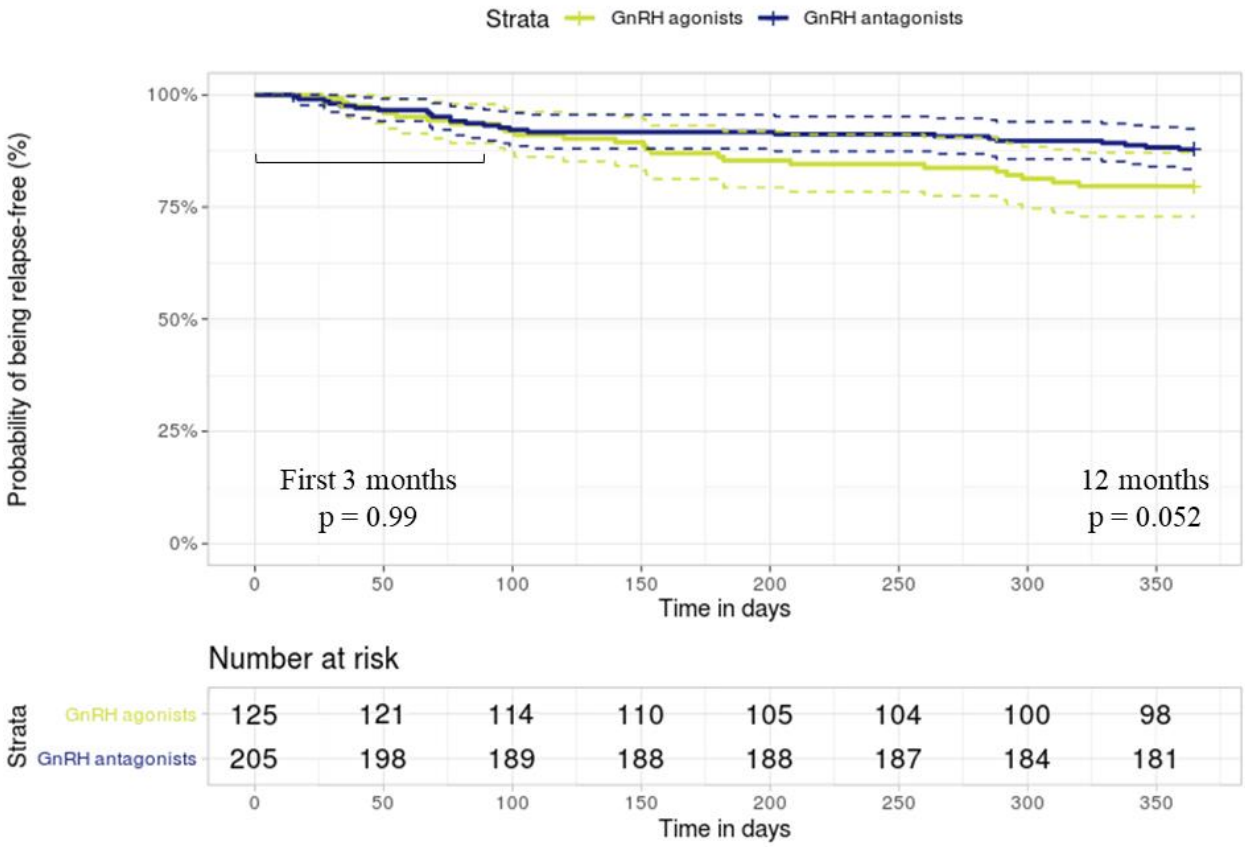
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Abbreviations: IVF, In Vitro Fertilization; ARR, Annualized Relapse Rate
*3 months before IVF; **3 months one year before IVF

Figure 2. Incidence Rate Ratio of relapse to two control periods: main analysis and control period.

Figure 3. Time from In Vitro Fertilization (IVF) to first relapse within 12 months according to the stimulation protocol.



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