RESEARCH ARTICLE OPEN ACCESS

Inflammatory Activity After Diverse Fertility Treatments

A Multicenter Analysis in the Modern Multiple Sclerosis Treatment Era

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Neurol Neuroimmunol Neuroinflamm 2023;10:e200106. doi:10.1212/NXI.0000000000200106

Abstract

Background and Objectives

Patients with multiple sclerosis (MS) may seek fertility treatment (FT)—including in vitro fertilization (IVF). Variable relapse risk after IVF has been reported in small historical cohorts, with more recent studies suggesting no change in annualized relapse rate (ARR). The objective of this study was to evaluate ARR 12 months pre-FT and 3 months post-FT in a multicenter cohort and identify factors associated with an increased risk of relapse.

Methods

Patients with clinically isolated syndrome (CIS) or MS aged 18–45 years with at least 1 FT from January 1, 2010, to October 14, 2021, were retrospectively identified at 4 large academic MS centers. The exposed period of 3 months after FT was compared with the unexposed period of 12 months before FT. FTs included controlled ovarian stimulation followed by fresh embryo transfer (COS-ET), COS alone, embryo transfer (ET) alone, and oral ovulation induction (OI). The Wilcoxon signed rank test and mixed Poisson regression models with random effects were used to compare ARR pre-FT vs post-FT, with the incidence rate ratio (IRR) and 95% CI reported.

Results

One hundred twenty-four FT cycles among 65 patients with MS (n = 56) or CIS (n = 9) were included: 61 COS-ET, 19 COS alone, 30 ET alone, and 14 OI. The mean age at FT was 36.5 ± 3.8 years, and the mean disease duration was 8.2 ± 5.0 years. Across 80 cycles with COS, only 5 relapses occurred among 4 unique patients within 3 months of treatment. The mean ARR after COS and before was not different (0.26 vs 0.25, $p = 0.37$), and the IRR was 0.95 (95% CI: 0.52–1.76, $p = 0.88$). No cycles with therapeutic disease-modifying therapies (DMTs) during COS had 3 months relapse (ARR 0 post-COS vs 0.18 pre-COS, $p = 0.02$, n = 34). Relapse rates did not vary by COS protocol. Among COS-ET cycles that achieved pregnancy (n = 43), ARR decreased from 0.26 to 0.09 ($p = 0.04$) within the first trimester of pregnancy. There were no relapses 3 months after ET alone and 1 relapse after OI.

Discussion

In this modern multicenter cohort of patients with MS undergoing diverse FTs, which included 43% on DMTs, we did not observe an elevated relapse risk after FT.

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Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

Glossary

AMH = anti-Mullerian hormone; **ARR** = annualized relapse rate; **BMI** = body mass index; **COS** = controlled ovarian stimulation; **DMTs** = disease-modifying therapies; **EDSS** = Expanded Disability Status Scale; **EMR** = electronic medical record; **ET** = embryo transfer; **FTs** = fertility treatments; **GnRH** = gonadotropin-releasing hormone; **IRR** = incidence rate ratio; **IUI** = intrauterine insemination; **IVF** = in vitro fertilization; **MS** = multiple sclerosis; **NU** = Clinical Neuroimmunology Center; **OI** = ovulation induction; **RRMS** = relapsing-remitting multiple sclerosis; **UCSF** = University of California San Francisco Center for MS and Neuroinflammation.

Understanding the impact of fertility treatments (FTs) on multiple sclerosis (MS) disease activity represents a treatment goal because impaired fecundity affects approximately 11% of the female reproductive age population in the United States.[1] While women with MS are more likely to receive an infertility diagnosis, they are less likely to receive FT.[2] Historically, 5 small studies (N = 4–32) reported an elevated relapse risk in women with MS after assisted reproductive technologies.[3-7] Specific contributing factors seemed to include the use of gonadotropin-releasing hormone (GnRH) agonists and failure to conceive. These findings were supported by a meta-analysis and pooled analysis of the individual studies.[8] However, more recent and larger cohort studies have failed to demonstrate an increased risk of relapse.[8,9] Possible explanations for these conflicting results include changes in stimulation protocols over time, including a shift from GnRH agonist to GnRH antagonist–based protocols and an increased use of disease-modifying therapies (DMTs) throughout FT. These trends warrant further evaluation among patients with MS pursuing FTs.

In addition, there is a need for a broader analysis that encompasses the full spectrum of currently available FTs. Most cohort studies to date have focused on the risks associated with conventional in vitro fertilization (IVF), consisting of controlled ovarian stimulation followed by oocyte retrieval and IVF with fresh embryo transfer (COS-ET). However, patients may pursue other assisted reproductive treatments, including COS and oocyte retrieval without subsequent embryo transfer (ET) for the purposes of oocyte or embryo cryopreservation or ET without COS when using cryopreserved autologous oocytes or embryos or embryos derived from donor oocytes. Patients may also pursue ovulation induction (OI) with oral agents such as clomiphene citrate or letrozole, followed by timed intercourse or intrauterine insemination (IUI).

To capture the full scope of fertility care, the current analyses evaluated the effect of various FTs on MS course in a contemporary cohort, leveraging data from 4 individual MS centers in the United States. Our primary aim was to evaluate the hypothesis that there was no increase in annualized relapse rate (ARR) after vs before FT. Our secondary aim was to evaluate the role of patient, MS, DMT, and FT-related factors on relapse risk.

Methods

Study Design and Setting

This was an observational retrospective evaluation of data collected at 4 tertiary care MS centers in the United States: Northwestern University MS and Clinical Neuroimmunology Center (NU), University of California San Francisco Center for MS and Neuroinflammation (UCSF), the Brigham MS Center (Brigham), and the University of Pennsylvania MS & Related Disorders Center (UPenn). In this cohort, the ARR 3 months after exposure to FT was compared with the unexposed period of 12 months before FT. Investigators collected data at each site using a standardized data entry form and deidentified earlier secure transfer to the primary site, NU.

Participants

Patients with clinically isolated syndrome (CIS) or MS as defined by the diagnostic criteria when care was provided, between the ages of 18 and 45 years, were included.[10-12] Patients must have undergone at least 1 COS, ET, or OI cycle between January 1, 2010, and September 14, 2021. Patients were excluded if they had previously received cyclophosphamide because it can reduce fertility and if the onset of CIS or MS was after FT.

Procedures

At NU, UPenn, and UCSF, an electronic medical record (EMR) search was performed using the billing diagnosis code of MS (G35) between ages 18 and 55 years. This group was then screened for billing diagnosis codes related to pregnancy and fertility. Records were then manually searched to find all patients with MS who had undergone FT during the study period. At Brigham MS Center, patients were identified based on both research database and EMR query, cross-referencing relevant diagnostic and procedure codes. Records were then manually searched for the confirmation of diagnoses and procedures for the study period in question. To reduce clinician recall bias or other forms of selection bias, a systematic search of the medical record was performed at each Center.

Standard Protocol Approvals, Registrations, and Patient Consents

The primary study site for data collation and statistical analysis was Northwestern University, whose Institutional Review Board approved the retrospective analysis of EMR-derived data (STU00214521). Each contributing site received local

ethical board approval for EMR review and sharing of deidentified data. This study was exempt from the requirement of participant consent at all sites.

Data Availability

Data not provided in the article because of space limitations may be shared (anonymized) at the request of a qualified investigator for purposes of replicating procedures and results. Data will be made available up to 3 years after publication of this article. The authors will share the data with investigators whose proposal of data use has been approved by an independent review committee and with whom a data sharing agreement has been signed.

Demographic and Clinical Data Collection

Coinvestigators at each site extracted demographic, MS clinical data, and fertility data from the EMR and research databases. In cases where date was unknown (i.e., MS diagnosis date), the month was approximated as July and/or date as the 15th.

Demographic data collected were as follows: date of birth, race, ethnicity, body mass index (BMI, kg/m^2), gravidity, parity, and comorbidities during FT.

MS clinical history included date of MS onset, MS type at FT cycle (CIS, relapsing remitting multiple sclerosis, primary progressive multiple sclerosis, secondary progressive multiple sclerosis), Expanded Disability Status Scale (EDSS)[13] at FT cycle (either listed or extrapolated by MS physician (E.G., R.B., M.H., T.B.K., and D.J.), when able), number of relapses in the year before assisted reproductive technology, date of most recent relapse, DMT within the prior 12 months, DMT stop date, date of first relapse post-FT, number of relapses within 3, 6, 9, and 12 months post-FT. When available, reports of MRI of the brain, cervical spine, and thoracic spine obtained in the year pre-FT and post-FT were reviewed for evidence of new T2 lesions or gadolinium-enhancing lesions.

DMT Presumed Biologic Activity

DMTs were categorized based on presumed biological activity during FT. Patients were considered to be on therapeutic DMT if they had received rituximab or ocrelizumab in the prior 6 months; dimethyl fumarate, diroximel fumarate, glatiramer acetate, or interferon treatment through the cycle. Natalizumab and S1P modulators were considered therapeutic only if they were continued throughout the cycle due to the risk of rebound relapse.[14]

FT Data Collection

Data included FT type (vide infra), date of gonadotropin start (if COS) and/or date of ET, outcome of cycle (not pregnant, biochemical, ectopic, pregnant, no ET performed), outcome of pregnancy (spontaneous abortion, therapeutic abortion, live birth), date of pregnancy end, gestational age, and when available, baseline anti-Mullerian hormone (AMH) and peak estradiol during stimulation.

FT Types

To evaluate the impact on MS relapse rate, FTs were divided as follows based on presumed impact on hormonal levels (Figure 1):

1. COS-ET: COS with egg retrieval followed by fresh ET, commonly referred to as IVF. During COS, the ovaries are stimulated with exogenous gonadotropins to produce multiple follicles, frequently resulting in estradiol levels greater than 10 times those of a typical menstrual cycle.[15]
2. COS: COS without fresh ET. This may occur when there are no embryos suitable for transfer or when the intent is to cryopreserve eggs or embryos for future use. As with COS-ET, estradiol levels are typically markedly elevated.
3. ET: ET without COS, as when using embryos derived from donor oocytes or cryopreserved autologous oocytes or embryos. Standard ET protocols either use the patient's natural menstrual cycle or hormonal preparations that closely approximate the patient's natural menstrual cycle, so estradiol levels are typically not markedly elevated. Rarely, GnRH agonists may be used with ET.
4. OI: Oral OI (letrozole/clomiphene) with or without IUI. Letrozole and clomiphene exert antiestrogenic effects, leading to increased follicle-stimulating hormone release and ovarian stimulation.[16] Estradiol levels may be elevated but are typically lower than those among gonadotropin COS cycles.

COS Subtypes

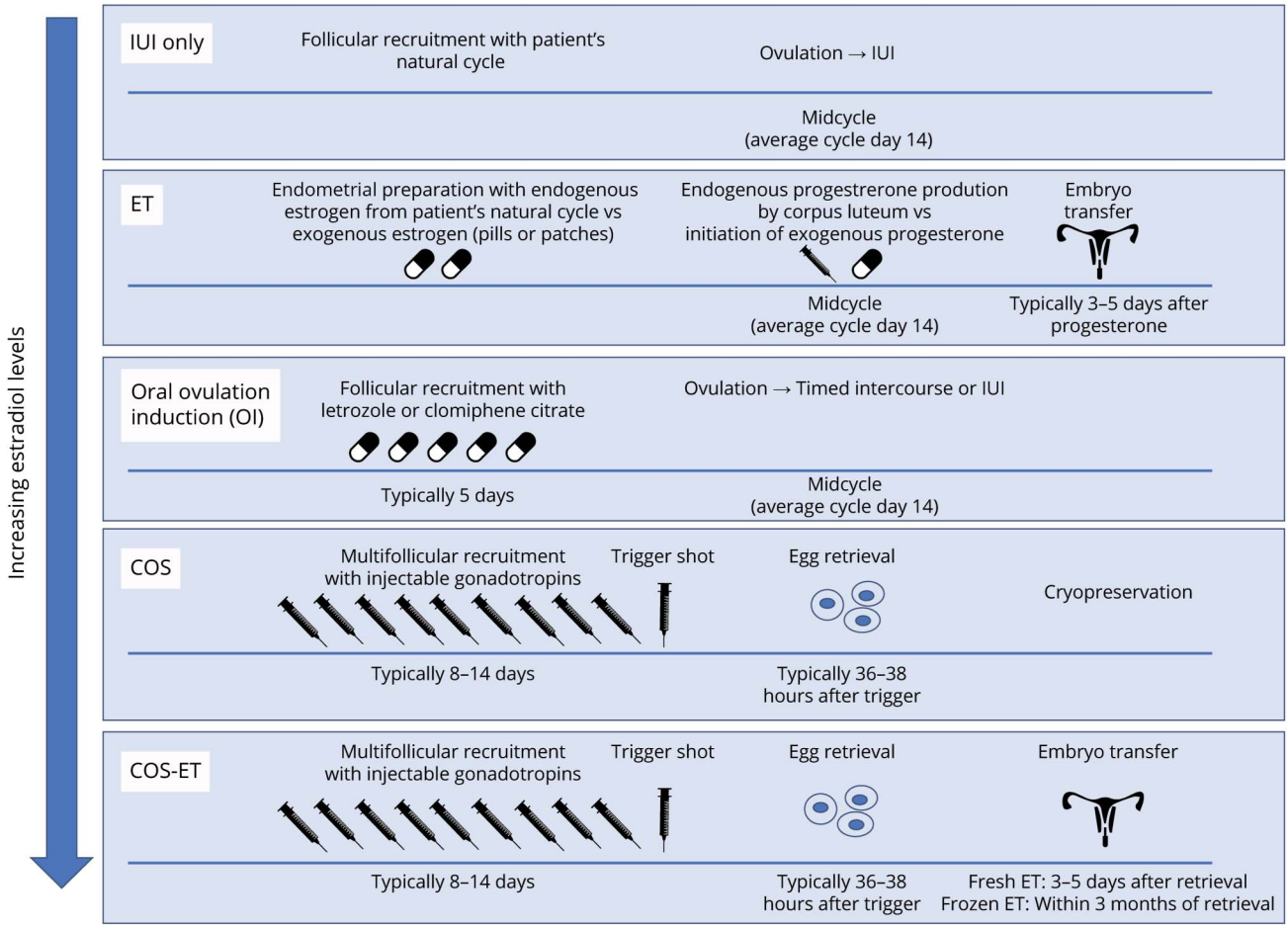
COS protocols were categorized according to their likely hormonal impact. The patient's endogenous ovulatory surge is prevented during the cycle using a GnRH agonist or GnRH antagonist. For patients with limited response to typical regimens, other protocols may be used, including administration of small doses of GnRH agonist throughout the stimulation ("flare" or "microdose flare" protocols), estrogen patch plus GnRH antagonist ("estrogen-priming" protocol), or small doses of gonadotropins ("mini stim").[17,18]

Statistical Analysis

The primary outcome was ARR in the 3 months post-FT compared with that in the 12 months before FT, with primary FT cycles of interest involving COS (COS-ET, COS only). The 3-month time frame after FT was selected because the 12-month timeframe could be confounded by other factors such as pregnancy occurrence, DMT resumption, or additional FT cycles. ARR is defined as the total number of relapses divided by the total person-time at risk of relapse. The Wilcoxon signed rank test for paired samples was used to compare median ARR 12 months before 3 months post–COS ± ET. This accounts for a paired sample within a cycle but does not account for clustering within patients across cycles.

To account for repeated measures of an individual over multiple cycles, generalized linear mixed effects models with

Figure 1 Overview of Common Fertility Treatments, Organized Based on Hypothetical Risk of MS Inflammatory Activity



MS = multiple sclerosis.

Poisson distribution that included a fixed effect for time and random intercept for patients were used to assess the ARR 3 months after vs 12 months before FT. The incidence rate ratio (IRR) for ARR 3 months post-FT compared with that 12 months pre-FT informs risk direction. If IRR is < 1, the rate of relapse was lower 3 months after FT. If IRR is > 1, the rate was higher 3 months after FT. If IRR is 1 or close to 1, there was no difference. Analyses were performed in the overall study population and stratified by demographic, clinical, and protocol-specific subgroups. The Wilcoxon rank sum test was used to assess the impact of relapse after the first cycle on future FTs.

Sensitivity analyses were performed to evaluate which demographic, clinical, and protocol-specific variables might be associated with elevated risk of relapses. For this analysis, our outcome was any relapse within 3 months and was limited to the first cycle. Logistic regression models assessed individual factors that were associated with increased odds of relapse within 3 months. Demographic variables were categorized dichotomously as follows: age (older than or younger than 37 years), race (White/Asian vs Black/Hispanic), BMI (greater than or less than 25 kg/m^2), and parity. Covariates were chosen based on those identified as relevant in the literature on MS activity after pregnancy and FT.[6-9,14] Age older than or younger than 37 years was based on the mean age of 36.5 years in the study group. The 6 Asian patients were grouped with the White patients because in our clinical experience, the disparities in MS outcomes noted for Black and Hispanic patients are not as marked in Asian American patients. MS disease-specific variables included disease type, new T2 lesions in prior year, and current DMT treatment (within past 12 months). Protocol-specific factors included FT protocol (COS-ET, COS only, ET only, and OI), COS protocol (GnRH agonist vs GnRH antagonist), estradiol level if known, number of stimulations within 3-month cycle, and FT outcome (pregnant, not pregnant, and no egg transfer/egg banking).

All statistical analyses were conducted using R statistical software (version 4.1.2).[19] Statistical significance threshold was set at $p < 0.05$.

Results

Participants

Altogether, data were collected on 124 FT cycles from 65 individual patients. The mean (SD) age at FT was 36.3 (4.4) years (range 24.7–46.7). Most of the patients were White (43, 78%); 7 (13%) were Black, 4 (7%) were Asian, and 1 (2%) was Hispanic. All patients had relapsing onset MS (56) or CIS (9); none had progressive MS. The mean (SD) disease duration was 7.7 (5.2) years (range 0.2–20.2). The median EDSS during FT was 1.0 (interquartile range 0.0–2.0). Demographic data and baseline patient characteristics are summarized in Table 1.

All FTs

Altogether, 124 FT cycles were collected for 65 individual women. FTs cycles were as follows: 61 COS-ET (49%), 19 COS only (15%), 30 ET only (24%), and 14 (11%) OI with letrozole or clomiphene. Most women contributed to only 1 type of FT, but 19 (29%) contributed 2+ types of FT cycles. The number of women contributing to each FT group was as follows: COS-ET (n = 43), COS only (n = 17), ET only (n = 17), and OI (n = 10). Regarding reasons for FT, 46 (71%) patients underwent treatment for infertility or a need for preimplantation genetic testing and 19 (29%) for fertility preservation. Patients undergoing OI were more likely to have 2 or more stimulations cycles per 3-month period (57%) than those undergoing COS-ET (21%) or COS only (26%).

For all FT cycles combined, 46 cycles (37%) resulted in pregnancy with live birth. COS-ET had the highest pregnancy success rate (n = 29, 48%), and OI had the lowest rate of pregnancy success (n = 3, 21%). Characteristics of individual treatment cycles are summarized in Table 2.

Table 1 Overview of Patient Demographics and Fertility Treatments

	COS and/or ET	OI	ALL
Total patients	55	10	65
Age at first fertility treatment, y (mean, SD)	35.9 (4.1)	38.8 (5.3)	36.3 (4.4)
Race/ethnicity (N, % patients)			
White	43 (78%)	8 (80%)	51 (78%)
Black	7 (13%)	0	7 (11%)
Asian	4 (7%)	2 (20%)	6 (9%)
Hispanic	1 (2%)	0	1 (2%)
BMI before fertility treatment, kg/m^2 (N, % patients)			
<18.5	1 (2%)	0	1 (2%)
18.5–24.9	32 (58%)	4 (40%)	36 (55%)
25–29.9	10 (18%)	5 (50%)	15 (23%)
>30	9 (16%)	1 (10%)	10 (15%)
Unknown	3 (5%)	0	3 (5%)
Disease course (N, % patients)			
CIS	7 (13%)	2 (20%)	9 (14%)
RRMS	48 (87%)	8 (80%)	56 (86%)
Duration of MS, y (mean [SD])	7.6 (4.8)	8.0 (7.1)	7.7 (5.2)
EDSS at fertility treatment (median, IQR)	1.0 (0.0–2.0)	1.25 (0.25–1.5)	1.0 (0.0–2.0)
Parity at first cycle (N, % patients)			
Nulliparous	44 (80%)	6 (60%)	50 (77%)
Parous	11(20%)	4 (40%)	15 (23%)
Average peak estradiol (pg/mL) (n = 67 stim cycles)	1959	n/a	n/a
Average AMH (ng/mL)	2.86	n/a	n/a

Abbreviations: AMH = anti-Mullerian hormone; ART = assisted reproductive technology; BMI = body mass index; CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; IQR = interquartile range; OI = ovulation induction, RRMS = relapsing-remitting multiple sclerosis.

Table 2 Characteristics of Individual Treatment Cycles

	COS and/or ET		OI		ALL
Total cycles	110		14		124
Total patients	55		10		65
Fertility treatment (total cycles analyzed)	**COS + ET[a]**	**COS only**	**ET only**	**OI ± IUI**	
Total cycles	61	19	30	14	124
# COS per 3-mo cycle					
0 (ET only)	n/a	n/a	30	n/a	30 (24%)
1	48 (79%)	14 (74%)	0	6 (43%)	68 (55%)
2 or more	13 (21%)	5 (26%)	0	8 (57%)	26 (21%)
COS protocol (N, % of stimulation cycles)					
GnRH antagonist	41 (67%)	11 (58%)	n/a	n/a	52 (65%)
GnRH agonist	11 (18%)	2 (11%)	n/a	n/a	13 (16%)
Flare	1 (2%)	4 (21%)	n/a	n/a	5 (6%)
Mini Stim	1 (2%)	1 (5%)	n/a	n/a	2 (3%)
Unknown	7 (11%)	1 (5%)	n/a	n/a	8 (10%)
Fertility treatment outcome (per cycle) (N, % of total cycles)					
Live birth or currently pregnant	29 (48%)	n/a	14 (47%)	3 (21%)	46 (44%)
Not pregnant, biochemical or early SAB	29 (48%)	n/a	16 (53%)	11 (79%)	56 (45%)
No ET (egg banking or no egg for transfer)	1 (2%)[a]	19 (100%)	n/a	n/a	20 (16%)
Unknown	2 (3%)	0	0	0	2 (2%)
DMT within 12 mo before fertility treatment					
Yes	37 (61%)	13 (68%)	13 (43%)	12 (86%)	75 (60%)
No	24 (39%)	6 (32%)	17 (57%)	2 (14%)	49 (40%)
DMT in 12 mo before fertility treatment (N, % of total cycles)					
Glatiramer acetate, Interferon	24 (39%)	2 (11%)	3 (10%)	6 (43%)	35 (28%)
Ocrelizumab, rituximab	7 (11%)	6 (32%)	4 (13%)	6 (43%)	23 (19%)
Dimethyl fumarate, diroximel fumarate	3 (5%)	0	6 (20%)	0	9 (7%)
Natalizumab	0	3 (16%)	0	0	3 (2%)
Fingolimod	3 (5%)	2 (11%)	0	0	5 (4%)
None in prior 12 mo	24 (39%)	6 (32%)	17 (57%)	2 (14%)	49 (40%)
DMT considered therapeutic during fertility treatment[b] (N, % of total cycles)					
Yes	23 (38%)	11 (58%)	8 (27%)	11 (79%)	53 (43%)
No or no treatment	38 (62%)	8 (42%)	22 (73%)	3 (21%)	71 (57%)
ARR in 3 mo posttreatment	0.13	0.63	0	0.28	0.19
ARR in 12 mo posttreatment	0.11	0.16	0.10	0.14	0.12
New MRI lesions in 12 mo post-FT	N = 31	N = 12	N = 15	N = 8	N = 66
Yes	6 (19%)	3 (25%)	3 (20%)	3 (37%)	15 (23%)
No	25 (81%)	9 (75%)	12 (80%)	5 (63%)	51 (77%)

Abbreviations: ARR = annualized relapse rate; COS = controlled ovarian stimulation; DMT = disease-modifying therapy; ET = embryo transfer; GnRH = gonadotropin-releasing hormone; IUI = intrauterine insemination; OI = oral ovulation induction; SAB = spontaneous abortion.
[a] One patient did not have embryo for transfer.
[b] Interferon, glatiramer acetate, fingolimod, natalizumab continued through fertility treatment. B cell–depleting agent infused within 6 months.

In the 12 months pre-COS and post-COS, DMT categories before each FT cycle were as follows: none (49, 40%), glatiramer acetate (24, 19%), ocrelizumab or rituximab (23, 19%), dimethyl fumarate, diroximel fumarate (9, 7%), and interferons (11, 9%); 8 were on medications associated with discontinuation rebound: fingolimod (5) and natalizumab (3).

Clinical Relapses

When accounting for all types of FT cycles, including ET-only cycles (n = 30) and OI (n = 14), 6 relapses occurred within the 3 months after FT in 124 cycles (5%) and 15 relapses occurred within the 12 months after FT (12%).

MRI Inflammatory Activity

Brain MRIs were available for 66 cycles; 23% of brain MRIs obtained within 12 months after FT revealed new brain lesions; 19% after COS-ET, 25% after COS only, 20% after ET only, and 37% after OI. These data are presented descriptively because numbers were low due to timing of MRI acquisition relative to FT, and indications for acquisition were variable across participating sites. The proportion of patients obtaining an MRI among those who failed FT or did not attempt pregnancy (ET only) vs those who had pregnancy was not different (57% vs 45%, Pearson χ^2 $p = 0.24$).

COS Cycles Only

The primary statistical analysis focused on patients undergoing COS with or without ET, in keeping with prior cohorts analyzed and focusing on treatments with the greatest impact on hormone levels. Therefore, COS-ET (n = 61) and COS only (n = 19) were included in this analysis. Multiple stimulations within 3 months were counted as 1 COS cycle for the purpose of relapse analysis. Patients underwent an average of 1.3 stimulations per 3-month cycle (range 1–4).

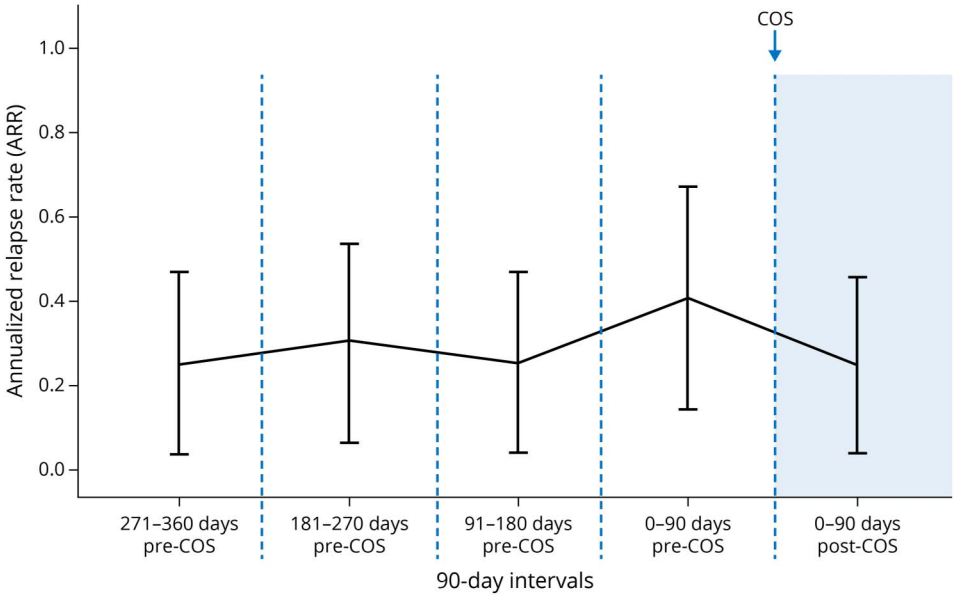
Clinical Relapses

Altogether, for the 80 individual COS cycles, 5 relapses in 4 unique patients occurred within 3 months post-FT. The mean ARR after COS and before was not different (0.26 vs 0.25, $p = 0.37$), and the IRR was 0.95 (95% CI: 0.52–1.76, $p = 0.88$). When looking at the full 12 months after COS, 13/55 (24%) patients experienced a relapse: 5/55 (5%) within 3 months, 2/55 (4%) within 3–6 months, 4/55 (8%) within 6–9 months, and 2/55 (4%) within 9–12 months of COS.

Given 29 (36%) patients undergoing COS cycles had a prior stimulation within 12 months, we performed an additional analysis to ensure there was no confounding due to repeated stimulation cycles within any observation period. This analysis was restricted to the 51 COS cycles without stimulation in the previous 12 months, and the ARR in the 3 months after COS relative to 12 months before remained unchanged (ARR 0.24 vs 0.37, $p = 0.12$). Figure 2 compares ARR 12 months pre-COS and 3 months post-COS for all cycles (n = 80).

There were 5 cycles (4 patients) with a relapse in the 3 months after COS. In 4 cases, the patient did not pursue additional COS cycles; 1 patient did and experienced a relapse after her subsequent treatment. There was no difference in the mean (1.5) and median (1) number of cycles between patients who had a relapse (n = 4) and those who did not relapse (n = 51) in 3 months after the first cycle of COS (Wilcoxon rank sum test with continuity correction: W = 104, $p = 0.95$).

Figure 2 Annualized Relapse Rate 3 Months Post-COS vs 12 Months Pre-COS for All Cycles (n = 80)



COS = controlled ovarian stimulation.

Effect of DMT

Being on therapeutic DMT during COS (n = 34) was associated with a lower relapse rate 3 months post-COS (0.18 vs 0, $p = 0.02$). All 5 patients who relapsed in the 3 months after COS were off DMT. Of the 13 patients who relapsed over the entire 12-month period post-COS, 10 were not on DMTs and 3 were on DMTs (glatiramer acetate-2, fingolimod-1).

None of the patients on natalizumab or fingolimod relapsed in the 3 months post-COS, and only 1 of the 8 patients relapsed in the 12 months before COS. For the 5 patients on fingolimod, 2 patients continued treatment through their COS-only cycle and the other 3 stopped treatment 4–11 months before COS-ET. Two patients on natalizumab continued infusions through their COS-only cycle; the other patient stopped natalizumab 9 months before COS only.

Subgroup Analyses of ARR Pre-COS and Post-COS in the COS ± ET Cycles

In the overall population and in most stratified analyses, ARR in the 12 months before and 3 months after COS ± ET were similar (Figure 3, Table 3).

MS and Demographic Factors

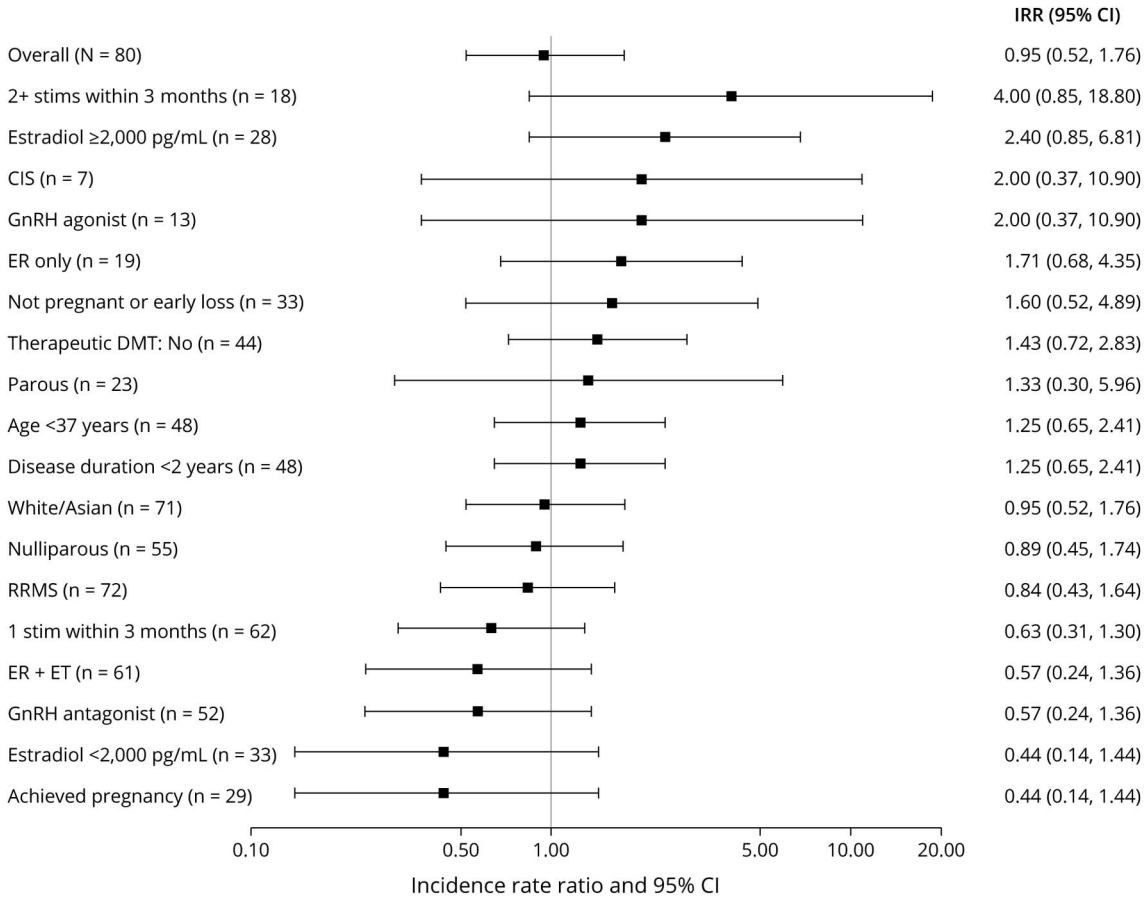
When evaluating ARR changes after COS in cycles among demographic or MS clinical subgroups, ARR in the 3 months after COS cycles was found to be significantly lower than before in several subgroups: age 37 years or older, MS disease duration at least 2 years, and those on therapeutic DMT (Table 3). Relapse risk did not seem to differ before and after COS according to other demographic or MS (race, BMI, and parity) characteristics.

COS Protocol Factors

When evaluating for FT protocol–related factors, there was a trend toward lower ARR post–COS-ET (0.23 vs 0.13, $p = 0.07$) and IRR 0.57 (95% CI: 0.24–1.36, $p = 0.21$). There was no significant difference in the ARR post–COS-only cycle relative to before (0.63 vs 0.37, $p = 0.61$). The IRR post–COS-only cycle was 1.71 (95% CI: 0.68–4.35, $p = 0.26$) (Table 3).

Use of GnRH agonist vs antagonist did not result in a difference in relapse rates: GnRH agonist IRR = 2 (95% CI: 0.37–10.9, $p = 0.42$) and GnRH antagonist IRR = 0.57 (95%

Figure 3 Annualized Relapse Rate 3 Months Post-COS vs 12 Months Pre-COS



Forest plot shows incidence rate ratio (IRR) overall and by subgroups. If IRR <1, rate of relapse was lower 3 months after FT. If IRR >1, rate is higher 3 months after FT. If IRR is 1, or close to 1, no difference. IRR was unable to be calculated for the following due to no relapses in these groups: age 37 years or older (n = 32), Black or Hispanic (n = 8), disease duration ≥2 years (n = 32), and patients on therapeutic DMT (n = 34). COS = controlled ovarian stimulation; FTs = fertility treatments.

Table 3 Comparison of ARR in the Year Before and 3 Months After COS Cycles With or Without ET (i.e., IVF and Embryo Banking)[a]

		Comparison ARR before vs after COS[b]					Effect on relapse rate[c]		
		ARR in 12 mo before FT		ARR in 3 mo after FT			IRR <1 = rate lower, IRR >1 = rate higher		
	N	Mean (SD)	Median (range)	Mean (SD)	Median (range)	*p* Value	IRR	95% CI	*p* Value
Overall	80	0.26 (0.54)	0 (0–3)	0.25 (0.97)	0 (0–4)	0.37	0.95	0.52–1.76	0.88
Age, y									
<37	48	0.33 (0.63)	0 (0–3)	0.42 (1.24)	0 (0–4)	0.94	1.25	0.65–2.41	0.51
≥37	32	0.16 (0.37)	0 (0–1)	0 (0)	0 (0–0)	**0.037**	—	—	—
Race									
White or Asian	71	0.30 (0.57)	0 (0–3)	0.28 (1.03)	0 (0–4)	0.37	0.95	0.52–1.76	0.88
Black or Hispanic	8	0 (0)	0 (0–0)	0 (0)	0 (0–0)	NaN	—	—	—
BMI, kg/m^2									
<25	49	0.22 (0.42)	0 (0–1)	0.33 (1.11)	0 (0–4)	0.90	1.45	0.68–3.13	0.34
= 25	27	0.37 (0.74)	0 (0–3)	0.15 (0.77)	0 (0–4)	20.17	0.4	0.13–1.27	0.12
MS course									
CIS	7	0.29 (0.49)	0 (0–1)	0.57 (1.51)	0 (0–4)	1	2	0.37–10.9	0.42
RRMS	72	0.26 (0.56)	0 (0–3)	0.22 (0.92)	0 (0–4)	0.24	0.84	0.43–1.64	0.61
MS duration									
<2 y	48	0.33 (0.63)	0 (0–3)	0.42 (1.24)	0 (0–4)	0.94	1.25	0.65–2.41	0.51
≥2 y	32	0.16 (0.37)	0 (0–1)	0 (0)	0 (0–0)	**0.037**	—	—	—
Parity									
Nulliparous	55	0.33 (0.61)	0 (0–3)	0.29 (1.05)	0 (0–4)	0.38	0.89	0.45–1.74	0.73
Parous	23	0.13 (0.34)	0 (0–1)	0.17 (0.83)	0 (0–4)	0.85	1.33	0.30–5.96	0.71
Therapeutic DMT during FT									
Yes	34	0.18 (0.39)	0 (0–1)	0 (0)	0 (0–0)	**0.02**	—	—	—
No	44	0.32 (0.64)	0 (0–3)	0.46 (1.28)	0 (0–4)	0.82	1.43	0.72–2.83	0.31
Fertility treatment									
COS-ET	61	0.23 (0.46)	0 (0–2)	0.13 (0.72)	0 (0–4)	0.07	0.57	0.24–1.36	0.21
COS only	19	0.37 (0.76)	0 (0–3)	0.63 (1.50)	0 (0–4)	0.61	1.71	0.68–4.35	0.26
COS protocol									
GnRH agonist	13	0.15 (0.38)	0 (0–1)	0.31 (1.11)	0 (0–4)	1	2	0.37–10.9	0.42
GnRH antagonist	52	0.27 (0.56)	0 (0–3)	0.15 (0.78)	0 (0–4)	0.10	0.57	0.24–1.36	0.21
# Stimulations within 3 mo									
1	62	0.31 (0.59)	0 (0–3)	0.19 (0.87)	0 (0–4)	0.12	0.63	0.31–1.30	0.21
≥2	18	0.11 (0.32)	0 (0–1)	0.44 (1.29)	0 (0–4)	0.58	4	0.85–18.8	0.08
Fertility outcome post-ET									
Achieved pregnancy	29	0.31 (0.54)	0 (0–2)	0.14 (0.74)	0 (0–4)	0.11	0.44	0.14–1.44	0.18
Not pregnant or SAB	33	0.15 (0.36)	0 (0–1)	0.24 (0.97)	0 (0–4)	0.93	1.6	0.52–4.89	0.41

Abbreviations: ARR = annualized relapse rate; CIS = clinically isolated syndrome; COS = controlled ovarian stimulation; DMT = disease-modifying therapy; ER = egg retrieval; ET = embryo transfer; GnRH = gonadotropin-releasing hormone; IRR = incidence rate ratio; IVF = in vitro fertilization; NaN = "not a number," unable to compare; RRMS = relapsing-remitting multiple sclerosis; SAB = spontaneous abortion.
Bold entries are *p* value <0.05 which was considered statistically significant.
[a] This table excludes the 30 embryo transfers from prior storage or donor egg.
[b] The Wilcoxon signed rank test for paired samples and does not take into account repeated patients/multiple cycles.
[c] Generalized linear mixed effects model with Poisson distribution and random intercept for participant (cycle nested within individual). Predictor is time (3 months after FT vs 12 months prior–referent, not shown). If IRR <1, rate of relapse was lower 3 months after FT. If IRR >1, rate is higher 3 months after FT. If IRR is 1, or close to 1, no difference.

CI: 0.24–1.36, $p = 0.21$) (Table 3). For cycles with 2 or more stimulations, ARR seemed numerically higher 3 months after COS compared with 12 months earlier (IRR 4.0; 95% CI: 0.85–18.8, $p = 0.08$, n = 18); 11 (58%) were on therapeutic DMT. There were very few relapses post-COS with those undergoing 1 stimulation cycle: ARR 0.31 pre-COS vs 0.19 post-COS ($p = 0.12$); IRR 0.63 (95% CI: 0.31–1.30, $p = 0.21$).

Referral Center

Most of the relapses (4) came from 1 referral center, which contributed the most patients, and which also had the lower proportion of patients on therapeutic DMT during FT (73%). Centers with >60% of patients on treatment at FT did not have patients who relapsed. We were underpowered to evaluate effects by site.

Estradiol Levels

Estradiol levels were available for 61 COS cycles. The low number of estradiol values available for cycles with relapses precluded statistical analyses of those data.

Non-COS Cycles

ET

Thirty patients underwent ET from prior frozen embryo (29) or egg donor (1). GnRH hormones were not used for ET in this cohort. This cohort had the lowest rate of therapeutic DMT use during treatment, but there were no relapses in the 3 months after ET (0/30, 0%).

Oral OI

Ten patients underwent 14 cycles of oral OI with letrozole (6) or clomiphene (8). Multiple rounds within a 3-month timespan were counted as 1 unique cycle for relapse analysis. Eight patients underwent multiple stimulations, with an average of 1.8 stimulations in a 3-month cycle (range 1–3 stimulations). After hormones were administered, 13 patients underwent IUI and 1 underwent timed intercourse. Overall, patients were on therapeutic DMT during 11/14 (79%) cycles. Only 1 relapse (1/14, 7%) occurred within the 3 months post-OI; the patient was not on DMT.

Outcome of FT

FT outcome was evaluated because prior studies suggested that the outcome of FT might influence the relapse rate after FT. For the COS-ET or ET-only cycles where pregnancy was not achieved, the ARR 3 months after FT was 0.24, which was not different from the pre-FT ARR of 0.15 ($p = 0.93$), with an IRR of 1.6 (95% CI: 0.52–4.89, $p = 0.41$).

For the COS-ET cycles where pregnancy was achieved (n = 29), ARR seemed to decrease after COS, although the difference was not statistically significant (0.14 3 months post-COS vs 0.31 12 months pre-COS, $p = 0.11$), with IRR 0.44 (95% CI: 0.14–1.44, $p = 0.18$). When including patients who achieved pregnancy from either COS + ET or ET only (n = 43), ARR decreased from 0.26 in 12 months before FT to 0.09 in the 3 months after FT ($p = 0.04$; IRR 0.36, $p = 0.083$). This suggested that achieving pregnancy after FT may be associated with a decrease in relapse risk, similar to the immunotolerant state observed after spontaneous pregnancies.

Discussion

This modern multicenter cohort identified no increase in relapse rate after FT in a group of women with recent or ongoing (43%) DMT use, regardless of FT type or hormonal protocol used. Over the past decade, there has been a trend for more active treatment for patients with MS of childbearing potential,[20] rendering more important the question of active DMT use during COS and oocyte harvesting procedures. In historical cohorts, few patients seeking FT were on DMT.[6,7] In a more recent French cohort where 24% of patients were treated with DMT during IVF, there was no difference in ARR 3 months before vs 3 months after IVF (0.20 vs 0.18). The percent of patients relapsing after IVF was lower in those on DMT (2% vs 9%).[9]

Overall, women with MS are more likely to be diagnosed with infertility, but less likely to receive FTs.[2] It is unclear whether the infertility diagnosis is related to biological causes because AMH levels seem to be similar between women with and without MS,[21] as does the median age of natural menopause.[22,23] However, MS-related changes in mood, activity, or libido could influence a patient's likelihood of conceiving.[24]

The need for timely conception off DMT may lead some patients with MS to seek FT earlier than the general population. For instance, women on B cell–depleting drugs such as ocrelizumab or rituximab are advised to conceive 3–6 months after infusion.[24] Therefore, the safety of FTs is a concern for many women with MS.

Small historical studies[3-7] and larger, more recent ones[8,9] primarily evaluated MS inflammatory activity after fresh IVF (COS-ET) cycles. In line with 2 more recent studies,[8,9] the current analysis identified no elevation in relapse rate after COS-ET cycles. Current COS protocols are typically shorter and more frequently use GnRH antagonists, but we also detected no elevation in relapses even when GnRH agonists were used. Furthermore, almost half of all patients were considered therapeutic on DMT during FT, reflecting a shift in MS care toward more active management of patients during periods of high relapse risk.[25]

In addition to evaluating the risk of relapse after COS-ET, we extend prior studies by evaluating inflammatory activity after other FTs that collectively encompass the full spectrum of modern fertility care. Increasingly, patients undergoing COS and egg retrieval may delay ET, to pursue a frozen ET at a later date, or oocyte or embryo cryopreservation for medical or social fertility preservation. Furthermore, ET from previously cryopreserved autologous eggs/embryos or embryos derived from donor eggs is increasingly common.[26-29] And while one

of the oldest FTs OI with clomiphene citrate or letrozole with or without IUI remains one of the most commonly used FTs nationwide. Each type of FT expands childbearing options. While the treatments involve varying degrees of hormonal preparation, a total of 6 relapses were observed within 3 months after 124 cycles.

While overall risk remains low for patients with MS undergoing FT, certain factors may be protective. Older age, which is known to be associated with declining risk of relapses in MS, is also associated with decreased success of FTs. Patients older than 37 years and with disease course longer than 2 years had a significantly lower relapse rate. Pregnancy remains a protective factor and may be one of the reasons why the COS-ET had a lower ARR post-FT because they were the most likely to achieve pregnancy. Remaining on DMT significantly lowered relapse risk for women undergoing COS. Finally, there were no relapses in the group of patients undergoing ET only, regardless of DMT status, which may be due to the lower exogenous hormonal exposure in this group.

The main limitation of this study is its retrospective nature, with relapses clinically defined and MRI confirmation of new disease activity only available in a subset of cases. It is possible that not all relapses were collected in the EMR. The retrospective nature also limited the availability of specific details about the FTs. Certain cycles of FTs could be underascertained, especially OI, because these cycles do not involve as intensive hormonal changes, do not have specific diagnostic codes, and may not be as likely to be reported to the neurologist. There may be site-based limitations because differential MS care may influence DMT timing relative to FT and FT selection may vary across referral sites. The low proportion of Black, Hispanic, or Asian patients may reflect differences in the utilization of FTs, in the documentation of FTs in the medical record, or in the proportion of women seeking care for their MS at the centers during the study period. Further studies are necessary to evaluate MS outcomes after FT in more diverse women. Finally, the heterogeneity of fertility cycles, a feature of modern FTs personalized to optimize individual outcomes and the low numerical count of relapses, limited statistical power to identify specific risk factors for relapses. This study was not powered to detect specific differences between groups, and these estimates have wide CIs, but the overall low number of relapses described here is informative and reassuring.

Patients with CIS/MS, along with the general population, may use FT to optimize conception in several clinical and social scenarios, including fertility preservation, older age, single parenting, male factor infertility, and same-sex relationships. As the use of FTs has evolved, so have questions about the optimal management of MS during these periods. The low risk of relapses in this contemporary treated cohort, confirms more recent reports.[8,9] Furthermore, our findings also provide reassurance to patients and fertility experts that the use of ET only and OI are not associated with elevated risk of relapses. In these settings aimed to promote conception, judicious use of DMTs will still be required to optimize MS disease stability and minimize fetal risk. Therapies with biological effects that persist beyond their elimination (e.g., induction therapies such as alemtuzumab, or B cell–depleting therapies) may achieve this therapeutic goal. Our findings highlight the importance of informed up-to-date management of patients with MS who seek fertility support. Of importance, continuing highly effective appropriately timed DMT during FTs may reduce the risk of relapse during this period of marked hormonal fluctuations and stressors.

Acknowledgment

The authors thank the talented investigators from Northwestern, UCSF, Brigham, and the University of Pennsylvania for their dedication to this project and to the patients who have entrusted them with their MS care.

Study Funding

Northwestern Neurology Department for statistical support; R. Bove funded by the NMSS Harry Weaver Award.

Disclosure

E. Graham received consulting and advisory board fees from Roche Genentech, Novartis, Atara Biotherapeutics, Tavistock Life Sciences. She receives research support from F. Hoffman-La Roche Ltd. She received compensation for question writing from ACP MKSAP; J.B. Bakkensen, A. Anderson, N. Lancki, A. Davidson, and G. Perez have nothing to disclose; C. Bevan has received advisory board fees from Genentech; E. Jungheim has nothing to disclose; A.C. Vanderhoff, B. Ostrem, E. Mok-Lin, and D. Huang have nothing to disclose; D. Jacobs has received consulting and advisory board fees from Biogen, Roche Genentech, Novartis, EMD Serono, Banner Life Sciences, Bristol Myers Squibb, Horizon, and Sanofi Genzyme. She has received research support from Genentech, Novartis, UCLA, and Biogen. UPenn has received fellowship support from EMD Serono; T.B. Kaplan has received consulting and advisory board fees from Roche-Genentech, Novartis, and Bristol Myers Squibb; M. Houtchens has received consulting income from Biogen, Novartis, Roche Genentech, Genzyme, and EMD Serono. She has also received research support from Biogen, Roche Genentech, Novartis, and Genzyme; R. Bove has received research funding from NIH, NMSS, DOD, NSF, Biogen, Roche Genentech, and Novartis. Consulting/advisory boards: Alexion, EMD Serono, Genzyme Sanofi, Jansen, Novartis, Roche Genentech, and TG Therapeutics. Go to Neurology.org/NN for full disclosures.

Publication History

Received by *Neurology: Neuroimmunology & Neuroinflammation* November 9, 2022. Accepted in final form February 6, 2023. Submitted and externally peer reviewed. The handling editor was Editor Josep O. Dalmau, MD, PhD, FAAN.

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References

1. *National Survey of Family Growth, Centers for Disease Control and Prevention [CDC] 2006-2010*. cdc.gov/nchs/data/series/sr_02/sr02_150.pdf.
2. Houtchens MK, Edwards NC, Hayward B, Mahony MC, Phillips AL. Live birth rates, infertility diagnosis, and infertility treatment in women with and without multiple sclerosis: data from an administrative claims database. *Mult Scler Relat Disord*. 2020; 46:102541. doi: 10.1016/j.msard.2020.102541.
3. Laplaud DA, Leray E, Barrière P, Wiertlewski S, Moreau T. Increase in multiple sclerosis relapse rate following in vitro fertilization. *Neurology*. 2006;66(8):1280-1281. doi: 10.1212/01.wnl.0000208521.10685.a6.
4. Hellwig K, Beste C, Brune N, et al. Increased MS relapse rate during assisted reproduction technique. *J Neurol*. 2008;255(4):592-593. doi: 10.1007/s00415-008-0607-2.
5. Hellwig K, Schimrigk S, Beste C, Muller T, Gold R. Increase in relapse rate during assisted reproduction technique in patients with multiple sclerosis. *Eur Neurol*. 2009; 61(2):65-68. doi: 10.1159/000177937.
6. Michel L, Foucher Y, Vukusic S, et al. Increased risk of multiple sclerosis relapse after in vitro fertilisation. *J Neurol Neurosurg Psychiatry*. 2012;83(8):796-802. doi: 10.1136/jnnp-2012-302235.
7. Correale J, Farez MF, Ysrraelit MC. Increase in multiple sclerosis activity after assisted reproduction technology. *Ann Neurol*. 2012;72(5):682-694. doi: 10.1002/ana.23745.
8. Bove R, Rankin K, Lin C, et al. Effect of assisted reproductive technology on multiple sclerosis relapses: case series and meta-analysis. *Mult Scler*. 2020;26(11):1410-1419. doi: 10.1177/1352458519865118.
9. Mainguy M, Tillaut H, Degremont A, et al. Assessing the risk of relapse requiring corticosteroids after in vitro fertilization in women with multiple sclerosis. *Neurology*. 2022;99(17):e1916-e1925. doi: 10.1212/WNL.0000000000201027.
10. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol*. 2001;50(1):121-127. doi: 10.1002/ana.1032.
11. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69(2):292-302. doi: 10.1002/ana.22366.
12. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173. doi: 10.1016/S1474-4422(17)30470-2.
13. Kappos L, D'Souza M, Lechner-Scott J, Lienert C. On the origin of Neurostatus. *Mult Scler Relat Disord*. 2015;4(3):182-185. doi: 10.1016/j.msard.2015.04.001.
14. Alroughani R, Alowayesh MS, Ahmed SF, Behbehani R, Al-Hashel J. Relapse occurrence in women with multiple sclerosis during pregnancy in the new treatment era. *Neurology*. 2018;90(10):e840-e846. doi: 10.1212/WNL.0000000000005065.

15. Stanczyk FZ, Clarke NJ. Measurement of estradiol–challenges ahead. *J Clin Endocrinol Metab*. 2014;99(1):56-58. doi: 10.1210/jc.2013-2905.
16. Kamath MS, George K. Letrozole or clomiphene citrate as first line for anovulatory infertility: a debate. *Reprod Biol Endocrinol*. 2011;9(1):86. doi: 10.1186/1477-7827-9-86.
17. Meyer M, Broughton D, Jungheim E. Best practices for controlled ovarian stimulation in in vitro fertilization. *Semin Reprod Med*. 2015;33(2):077-082. doi: 10.1055/s-0035-1546424.
18. Dragisic KG, Davis OK, Fasouliotis SJ, Rosenwaks Z. Use of a luteal estradiol patch and a gonadotropin-releasing hormone antagonist suppression protocol before gonadotropin stimulation for in vitro fertilization in poor responders. *Fertil Steril*. 2005;84(4):1023-1026. doi: 10.1016/j.fertnstert.2005.04.031.
19. R Core Team: A language and environment for statistical computing. R Project for Statistical Computing. Accessed May 17, 2022. www.R-project.org/.
20. Dobson R, Hellwig K. Use of disease-modifying drugs during pregnancy and breastfeeding. *Curr Opin Neurol*. 2021;34(3):303-311. doi: 10.1097/WCO.0000000000000922.
21. Graves JS, Henry RG, Cree BAC, et al. Ovarian aging is associated with gray matter volume and disability in women with MS. *Neurology*. 2018;90(3):e254-e260. doi: 10.1212/WNL.0000000000004843.
22. Bove R, Healy BC, Musallam A, Glanz BI, De Jager PL, Chitnis T. Exploration of changes in disability after menopause in a longitudinal multiple sclerosis cohort. *Mult Scler*. 2016;22(7):935-943. doi: 10.1177/1352458515606211.
23. Bove R, Healy BC, Secor E, et al. Patients report worse MS symptoms after menopause: findings from an online cohort. *Mult Scler Relat Disord*. 2015;4(1):18-24. doi: 10.1016/j.msard.2014.11.009.
24. Bove RM, Houtchens MK. Pregnancy management in multiple sclerosis and other demyelinating diseases. *Continuum (Minneap MN)*. 2022;28(1):12-33. doi: 10.1212/CON.0000000000001108.
25. Dobson R, Bove R. IVF and multiple sclerosis: evolving treatments and reducing relapse risk. *Neurology*. 2022;99(17):737-738. doi: 10.1212/WNL.0000000000201242.
26. Argyle CE, Harper JC, Davies MC. Oocyte cryopreservation: where are we now? *Hum Reprod Update*. 2016;22(4):440-449. doi: 10.1093/humupd/dmw007.
27. Stoop D, Nekkebroeck J, Devroey P. A survey on the intentions and attitudes towards oocyte cryopreservation for non-medical reasons among women of reproductive age. *Hum Reprod*. 2011;26(3):655-661. doi: 10.1093/humrep/deq367.
28. American Society for Reproductive Medicine (ASRM). More than 74 thousand babies born from assisted reproductive technology cycles done in 2018. 2020. asrm.org/news-and-publications/practice-committee-documents/additional-documents/references/more-than-74-thousand-babies-born-from-assisted-reproductive-technology-cycles-done-in-2018/.
29. Kawwass JF, Crawford S, Hipp HS, et al. Embryo donation: national trends and outcomes, 2000 through 2013. *Am J Obstet Gynecol*. 2016;215(6):747.e1-747.e5. doi: 10.1016/j.ajog.2016.06.050.

Inflammatory Activity After Diverse Fertility Treatments: A Multicenter Analysis in the Modern Multiple Sclerosis Treatment Era

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Neurol Neuroimmunol Neuroinflamm 2023;10;
DOI 10.1212/NXI.0000000000200106