Supplementary Tables.

Supplementary Table 1.

Summary of 5 published case series of relapse rates after assisted reproductive technology (ART) in women with multiple sclerosis.

Location	Design	Subjects, cycles	DMT cessation	Findings	Notes
France Study 1[8]	Single center retrospective	4 patients undergoing 6 IVF cycles, and 2 patients undergoing 4 IVF cycles	>1Y prior	Increased ARR in the 3 months after IVF (2.4+/- 2.8) vs. the 3 months (0 relapses) or 12 months (0.5+/-1.2) before IVF, or the 12 months after IVF (0.4+/-1.2).	Increased ARR was more prominent in the patients undergoing treatment with GnRH agonists (6) vs. antagonists (4).
France Study 2[9]	Multicenter retrospective	32 patients undergoing 70 IVF cycles	18 never used, 10 average discontinuation of 19 months prior, 4 continued treatment	Increased ARR in the 3 months post-IVF (1.60 ± 2.40) vs. the 3 months prior to IVF (0.80 ± 1.61) or the control period 1 year prior (0.68 ± 1.51)	Increased ARR 3 months post-IVF in cases of failure vs. in cases leading to pregnancy. In cases using GnRH antagonist, the pregnancy rate was lower (10% vs. 40%), but was not associated with increased ARR 3 months post- IVF,

					while there was an increased ARR in cases using GnRH agonists $(1.60 \pm 2.29$ 3 months post) vs. GnRH antagonists $(0.75 \pm 1.58$ 3 months prior)
Germany Study 1[10]	Nationwide retrospective	6 patients undergoing 14 ART cycles (5 IVF and 9 ICSI)		Significant increase in ARR 3 months post-ART (1.02 ± 0.86), as compared to 12 months pre-ART (0.29 ± 0.26). ARR increase was not dependent on gonadotropin used	5/6 subjects relapsed within 3 months post-ART
Germany Study 2[11]	Nationwide prospective and retrospective	14 prospective and 9 retrospective undergoing 78 cycles (32 IUI, 15 IVF, 31 ICSI)		Increased ARR in the 3 months post- ART (0.95 ± 0.12), compared to the 12 months pre-ART (0.62 ± 0.1). This increase was independent of gonadotropin used	IUI was associated with the greatest increase in ARR, with no effect of gonadotropin or time between stimulations. None of the 14 women who became pregnant experienced a relapse
Argentina[12]	Single center prospective	16 RRMS patients undergoing 26 ART cycles. All cycles used GnRH agonists, rFSH, and vaginal progesterone	$\geq$15 months	7-fold increased risk of relapses in the 3 months post-ART (75% patients, 58% cycles vs. 0% patients in the 9 months prior), and an increased ARR (3.28 at 3 months post vs. 0.42 in the 12 months prior and 9 months after)	9-fold increased risk of MRI activity, $(1.99 +/0 0.3$ new or enlarging T2 lesions 3 months post-ART) vs. $(0.36 \pm 0.2$ T2 lesions and 0.23 ± 0.1 Gd-enhancing lesions during the remaining observation period)

Supplementary Table 2.

Demographic and clinical characteristics of a cohort of 12 women who contributed 22 Assisted Reproductive Technology (ART) cycles for the analyses.

BOSTON cohort	Descriptive statistics of cohort
Subjects:	
Age	35.1 ± 3.60 (26,41)
Subjects; cycles	12; 22
Subjects contributing more than 1 cycle	50% (n=6 of 12 subjects)
DMT:	
Use before ART	63.6% (n=14 of 22 cycles)
Cessation before ART	100% (n=14 of 14 cycles)
Cessation time before ART	5.36 ± 4.41 months (0,12)
Parity:	
Nulliparity	63.6% (n=14 of 22 cycles)
Single	36.4% (n=8 of 22 cycles)
ART protocol:	
GnRH agonist	31.8% (n=7 of 22 cycles)
GnRH antagonist	9.09% (n=2 of 22 cycles)
Other	59.1% (n=13 of 22 cycles)
Disease:	
RRMS	83.3% (n=10 of 12 patients)
CIS	16.7% (n=2 of 12 patients)
ART outcome:	
No pregnancy	54.5% (n=12 of 22 cycles)
Term pregnancy	27.3% (n=6 of 22 cycles)
Miscarriage	4.55% (n=1 of 22 cycles)
Other	13.6% (n=3 of 22 cycles)

Supplementary Table 3.

Differences in the relapse count during the 3-month period before and after ART, in several stratified groups, in participants from Boston (12 participants, 22 cycles).

All ART	Coefficient	SE	p-value
Intercept	-1.73	4.58	0.71
3 months before vs. after ART	-1.10	1.15	0.34
Age at ART (years)	0.04	0.14	0.78
Disease duration (years)	-0.53	0.34	0.12
ART failure			
Intercept	-9.31	10.40	0.37
3 months before vs. after ART	-0.69	1.22	0.57
Age at ART (years)	0.25	0.29	0.39
Disease duration (years)	-0.53	0.33	0.10
GnRH agonists			
Intercept	-2.68	9.06	0.77
3 months before vs. after ART	-0.69	1.22	0.57
Age at ART (years)	0.07	0.25	0.77
Disease duration (years)	-0.36	0.26	0.17
Non-parity			
Intercept	-1.68	4.59	0.71
3 months before vs. after ART	-1.10	1.15	0.34
Age at ART (years)	0.04	0.14	0.80
Disease duration (years)	-0.46	0.35	0.19
No DMT before ART			
Intercept	-1.29	4.73	0.79
3 months before vs. after ART	-1.10	1.15	0.34
Age at ART (years)	0.02	0.14	0.89
Disease duration (years)	-0.22	0.36	0.53
DMT started more than 3 months after ART			
Intercept	-0.19	4.00	0.96
3 months before vs. after ART	-0.69	1.22	0.57
Age at ART (years)	-0.01	0.12	0.97
Disease duration (years)	-0.85	0.91	0.35

The analysis was performed with a mixed Poisson regression model, adjusted for the age at ART and disease duration at ART (modeled as fixed effects). Repetition of observations on the subject-level was modeled by random effect.

The coefficients represent the mean differences in the logarithm of the relapse count. Stratified groups with zero or near-zero variance in relapse count that could not be fitted to the Poisson regression model are excluded.

Supplementary Table 4.

Participants from Boston, France[9], Germany[11] and Argentina[12]: Differences between the ARR during the 1-year period before and 3-month period after ART, in several stratified groups.

All ART	Coefficient	SE	p-value
Intercept	-0.27	0.59	0.65
1 year before vs. 3 months after ART	1.31	0.08	3.6e-64
Age at ART (years)	-0.01	0.01	0.31
Disease duration (years)	-0.02	0.01	0.12
ART failure			
Intercept	-0.09	0.54	0.86
1 year before vs. 3 months after ART	1.37	0.09	1.4e-52
Age at ART (years)	-0.01	0.01	0.33
Disease duration (years)	-0.02	0.01	0.23
ART success			
Intercept	-0.55	0.99	0.58
1 year before vs. 3 months after ART	1.25	0.16	1.52e-14
Age at ART (years)	-0.01	0.02	0.66
Disease duration (years)	-0.04	0.03	0.20
GnRH agonists			
Intercept	-0.73	0.88	0.41
1 year before vs. 3 months after ART	1.35	0.11	2.12e-35
Age at ART (years)	0.02	0.02	0.50
Disease duration (years)	-0.06	0.03	0.02
GnRH antagonists			
Intercept	-1.09	4.22e-03	0.00e+00
1 year before vs. 3 months after ART	1.15	4.22e-03	0.00e+00
Age at ART (years)	6.95e-05	4.00e-03	0.99
Disease duration (years)	0.02	4.17e-03	1.11e-05
Neither agonists nor antagonists			
Intercept	-1.13	1.59	0.48
1 year before vs. 3 months after ART	1.33	0.13	2.17e-23
Age at ART (years)	-0.01	0.01	0.66
Disease duration (years)	-0.01	0.03	0.78

The analysis was performed with a mixed Poisson regression model, adjusted for the age at ART and disease duration at ART (modeled as fixed effects). Repetition of observations on the subject-level and site-level was modeled by random effects.

The coefficients represent the mean differences in the logarithm of the relapse count.

Supplementary Table 5.

Comparison of annualized relapse rate (ARR) in participants from Boston, France[9] and Argentina[12] in the 3-month period after ART, before ART, and 1 year before ART, in stratified groups.

GROUP	N	1 year before ART (ARR)			3 months after ART (ARR)			p-value
		Mean	Median	Range	Mean	Median	Range	
ALL CYCLES	**76**	**0.51**	**0**	**0-6**	**1.84**	**0**	**0-8**	**1.02e-04**
ART Outcome:								
• Failure	42	0.43	0	0-6	2.48	0	0-8	**1.50e-04**
• Success	30	0.43	0	0-3	1.07	0	0-8	0.16
ART Protocol:								
• GnRH agonists	57	0.56	0	0-6	2.39	0	0-8	**3.91e-05**
• GnRH antagonists	6	0.83	0.5	0-3	0.67	0	0-4	1.00
• Other	13	0.15	0	0-1	0.00	0	0-0	0.35
Parity:								
• Parous	8	0.00	0	0-0	0.00	0	0-0	NaN
• Nulliparous	40	0.28	0	0-2	2.20	0	0-8	**1.07e-03**
DMT:								
Prior to ART:								
• No DMT before ART	36	0.53	0	0-3	2.22	0	0-8	**0.01**
• DMT stopped >3 months before ART	43	0.47	0	0-6	2.33	0	0-8	**2.92e-04**
• DMT stopped < 3 months before ART	3	0.00	0	0-0	0.00	0	0-0	NaN
Following ART:								
• No DMT after ART	35	0.63	0	0-3	1.14	0	0-8	0.16
• DMT started >3 months after ART	28	0.39	0	0-2	1.14	0	0-8	0.14
• DMT started < 3 months after ART	11	0.55	0	0-6	5.82	8	0-8	**5.00e-03**

Supplementary Table 6.

Effect of ART on relapse rate in participants from Boston, France[9] and Argentina[12].
Differences between **the relapse count** during the 3-month period before and after ART, in several stratified groups.

All ART	Coefficient	SE	p-value
Intercept	-2.06	1.48	0.16
3 months before vs. after ART	1.48	0.39	**1.49e-04**
Age at ART (years)	0.01	0.04	0.84
Disease duration (years)	-0.12	0.05	**0.03**
ART failure			
Intercept	-2.18	2.09	0.30
3 months before vs. after ART	1.65	0.48	**6.45e-04**
Age at ART (years)	0.02	0.06	0.79
Disease duration (years)	-0.12	0.07	0.07
ART success			
Intercept	-1.23	2.51	0.62
3 months before vs. after ART	1.39	0.79	0.08
Age at ART (years)	-0.01	0.08	0.89
Disease duration (years)	-0.27	0.15	0.06
GnRH agonists			
Intercept	-2.12	1.44	0.14
3 months before vs. after ART	1.73	0.44	**8.96e-05**
Age at ART (years)	0.01	0.04	0.76
Disease duration (years)	-0.12	0.06	0.05
GnRH antagonists			
Intercept	-3.93	10.57	0.71
3 months before vs. after ART	1.24e-15	1.41	1.00
Age at ART (years)	0.02	0.32	0.94
Disease duration (years)	0.12	0.18	0.49
Nulliparous			
Intercept	-0.81	1.99	0.69
3 months before vs. after ART	1.99	0.61	**1.13e-03**
Age at ART (years)	-0.04	0.06	0.47
Disease duration (years)	-0.14	0.11	0.22
No DMT before ART			
Intercept	-2.67	1.82	0.14
3 months before vs. after ART	1.61	0.54	**2.92e-03**
Age at ART (years)	0.03	0.05	0.59
Disease duration (years)	-0.14	0.09	0.13
DMT stopped >3 months before ART			
Intercept	-0.32	2.22	0.89
3 months before vs. after ART	1.83	0.53	**5.89e-04**

Age at ART (years)	-0.04	0.06	0.50
Disease duration (years)	-0.14	0.10	0.15
No DMT after ART			
Intercept	-1.22	2.57	0.63
3 months before vs. after ART	0.92	0.59	0.12
Age at ART (years)	-0.02	0.08	0.83
Disease duration (years)	-0.10	0.08	0.24
DMT started >3 months after ART			
Intercept	-3.39	2.58	0.19
3 months before vs. after ART	1.39	0.79	0.08
Age at ART (years)	0.05	0.08	0.53
Disease duration (years)	-0.05	0.10	0.07
DMT started within 3 months after ART			
Intercept	5.78	4.07	0.16
3 months before vs. after ART	2.08	0.75	**0.01**
Age at ART (years)	-0.17	0.10	0.09
Disease duration (years)	-0.45	0.31	0.15

The analysis was performed with a mixed Poisson regression model, adjusted for the age at ART and disease duration at ART (modeled as fixed effects). Repetition of observations on the subject level and site level was modeled by random effects.

The coefficients represent the mean differences in the logarithm of the relapse count. Stratified groups with zero or near-zero variance in relapse count that could not be fitted to the Poisson regression model are excluded.

Abbreviations. ARR = annualized relapse rate. ART = assisted reproductive technology. DMT = disease modifying therapy.