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Diagnosis of infertility and infertility treatment in women with and without multiple sclerosis

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INTRODUCTION

- **Multiple sclerosis (MS) is three times more common in women than in men,[1] and the clinical onset is often during childbearing years.[2]**
- **There have been some reports suggesting that fertility in women with MS may be reduced.[3–6]**
- **Data regarding the diagnosis and treatment of infertility in women with MS compared with women without MS are lacking.**
- **The availability of health services utilization data, commonly referred to as administrative claims data, affords a unique opportunity to gain insight into the patient experience of care and relevant health outcomes in patients with MS across large, 'real-world' populations.[7]**
  - **A better understanding of the real-world outcomes of women with MS undergoing infertility treatment is essential to improve clinical support, healthcare services, and quality of life for this population.**

OBJECTIVE

- To compare the prevalence of infertility and the infertility treatments administered to women with and without MS, based on a United States retrospective commercial claims analysis.

METHODS

Data description

- This was a retrospective, administrative claims database study using IMS Health Real World Data Adjudicated Claims – US data between January 1, 2006 and December 31, 2015.
- The database comprises complete adjudicated plan-level data, including a complete inventory of individuals' prescriptions, inpatient hospital claims, and outpatient medical claims.
- The database consists primarily of commercial preferred provider organization plans.
  - Variations in treatments between the infertility practices and in the coverage of infertility benefit among different plans may not be appropriately reflected in the individual claims.
  - Administrative claims databases provide information on patients with health insurance; thus, findings may not be generalizable to patients undergoing *in vitro* fertilization who self-pay.
- Approximately 150 million individuals with a medical benefit, and a subset of 95 million individuals with both medical and pharmacy benefits, are included in the database.

Study population

- The database was used to identify US women with MS (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] diagnosis code: 340.xx), aged 18–55 years, with a minimum of 1 year of continuous insurance eligibility.

Infertility treatments utilized

- Oral infertility medications: clomiphene and/or letrozole.
- Injectable medications for controlled ovarian stimulation (COS), defined as ⩾1 gonadotropin (Gn) injection and an ovulation trigger, either human chorionic Gn or Gn-releasing hormone (GnRH) agonist, and other infertility treatments (Gn without trigger or GnRH antagonists).

Data analysis

- Women with MS were matched 1:1 to a pool of women without MS using exact matching.
- Matched characteristics were age group, census region, and index-year (year of entry into the database) quarter.
- For descriptive (i.e. unadjusted) analyses, categorical and binary variables were summarized using frequencies and percentages.
- Pairwise chi-square tests were conducted to evaluate significant differences in the prevalence of infertility diagnosis, treatments prescribed, and live births between women with and without MS.

RESULTS

Sample selection

- A total of 117,041 women with MS met the eligibility criteria.
- A comparator group of 1,422,836 women without MS was also selected.

Baseline characteristics

- Demographics and clinical characteristics for the original unmatched sample individuals are presented in **Table 1**.
- Demographics and clinical characteristics for the matched sample individuals are presented in **Table 2**.

Infertility treatments and live births

- The mean (standard deviation) duration of follow-up was 3.77 (2.36) years for women with MS and 3.82 (2.43) years for women without MS.
- In the matched cohort, a greater proportion of women with MS versus those without MS had a diagnosis of infertility (8.51% vs 8.08%; p=0.0006; **Table 3**).

Table 1. Demographic and clinical characteristics of women with and without MS

Variable	Women with MS (n=117,041)	Women without MS (n=1,422,836)
Age, years		
Mean (SD)	42 (9)	38 (10)
Median	43	38
Age grouping, years, n (%)		
18–30	15,888 (13.6)	434,175 (30.5)
31–34	10,979 (9.4)	142,224 (10.0)
35–37	10,028 (8.6)	110,859 (7.8)
38–40	11,272 (9.6)	113,983 (8.0)
41–42	8461 (7.2)	80,538 (5.7)
43–55	60,413 (51.6)	541,057 (38.0)
Geographic region, n (%)		
Midwest	33,319 (28.9)	376,831 (26.9)
Northeast	32,618 (28.3)	295,979 (21.1)
South	35,090 (30.4)	524,156 (37.4)
West	14,227 (12.3)	204,712 (14.6)
Insurance, n (%)		
Commercial	77,742 (66.4)	946,276 (66.5)
Medicaid	3515 (3.0)	60,470 (4.2)
Medicare	830 (0.7)	2811 (0.2)
Other	34,954 (29.9)	413,279 (29.0)
Comorbidity, n (%)		
Alcohol abuse	2033 (1.7)	27,768 (2.0)
Anxiety	32,069 (27.4)	307,829 (21.6)
Arthritis	22,724 (19.4)	204,095 (14.3)
Chronic lung disease	20,415 (17.4)	204,490 (14.4)
Depression	37,344 (31.9)	290,183 (20.4)
Diabetes	13,547 (11.6)	134,537 (9.5)
Gastrointestinal disorders	44,798 (38.3)	417,484 (29.3)
Hyperlipidemia	42,824 (36.6)	420,496 (29.6)
Hypertension	37,958 (32.4)	355,457 (25.0)
Thyroid disease	31,952 (27.3)	281,993 (19.8)

MS, multiple sclerosis; **SD**, standard deviation.

- A lower proportion of women with MS used any of the infertility treatments examined compared with women without MS (1.01% vs 1.19%; p=0.0002; **Table 3**).
- Of women receiving infertility treatments, more than half received oral infertility medications without Gn (54.9% of women with MS and 54.8% of women without MS; **Table 3**).
- The remaining women received either injectable COS medications (22.9% of women with MS vs 25.0% of women without MS) or other treatments (22.3% vs 20.2%, respectively; **Table 3**).
- The proportion of women using each of the individual infertility treatments was significantly lower in women with MS compared with women without MS ($p<0.05$), except for GnRH antagonists (**Table 3**).
- The rate of live births was significantly lower in women with MS than in women without MS (5.00% vs 6.98%; $p<0.0001$; **Table 3**).

Table 2. Demographic and clinical characteristics of the matched cohorts of women with and without MS

Variable	Women with MS (n=96,937)	Women without MS (n=96,937)
Age, years		
Mean (SD)	42 (9)	42 (9)
Median	43	43
Age grouping, years, n (%)		
18–30	13,302 (13.7)	13,302 (13.7)
31–34	9034 (9.3)	9034 (9.3)
35–37	8256 (8.5)	8256 (8.5)
38–40	9366 (9.7)	9366 (9.7)
41–42	7015 (7.2)	7015 (7.2)
43–55	49,964 (51.5)	49,964 (51.5)
Geographic region, n (%)		
Midwest	28,581 (29.5)	28,581 (29.5)
Northeast	25,480 (26.3)	25,480 (26.3)
South	32,574 (33.6)	32,574 (33.6)
West	10,302 (10.6)	10,302 (10.6)
Insurance, n (%)		
Commercial	64,686 (66.7)	65,255 (67.3)
Medicaid	2339 (2.4)	3417 (3.5)
Medicare	670 (0.7)	211 (0.2)
Other	29,242 (30.2)	28,054 (28.9)
Comorbidity, n (%)		
Alcohol abuse	1613 (1.7)	1841 (1.9)
Anxiety	26,383 (27.2)	20,992 (21.7)
Arthritis	19,048 (19.6)	16,507 (17.0)
Chronic lung disease	16,955 (17.5)	14,424 (14.9)
Depression	31,145 (32.1)	19,863 (20.5)
Diabetes	11,411 (11.8)	10,375 (10.7)
Gastrointestinal disorders	37,613 (38.8)	28,961 (29.9)
Hyperlipidemia	36,058 (37.2)	33,432 (34.5)
Hypertension	32,042 (33.1)	28,395 (29.3)
Thyroid disease	26,612 (27.5)	21,094 (21.8)

MS, multiple sclerosis; **SD**, standard deviation.

Table 3. Infertility treatments and live births in the matched cohort

Variable, n (%)	Women with MS (n=96,937)	Women without MS (n=96,937)	p value
Infertility diagnosis	8254 (8.5)	7837 (8.1)	0.0006
Infertility treatment	979 (1.0)	1150 (1.2)	0.0002
Clomiphene	408 (0.4)	473 (0.5)	0.0307
Letrozole	302 (0.3)	360 (0.4)	0.0265
Gn	234 (0.2)	298 (0.3)	0.0062
hCG	343 (0.4)	415 (0.4)	0.0098
Leuprolide	290 (0.3)	345 (0.4)	0.0397
GnRH agonist	294 (0.3)	347 (0.4)	0.0397
GnRH antagonist	111 (0.1)	124 (0.1)	0.4335
Oral treatment and no Gn	537 (0.6)	630 (0.6)	0.0069
Gn and trigger treatments	224 (0.2)	288 (0.3)	0.0053
Other infertility treatment (not oral treatment and not Gn and trigger treatments)	218 (0.2)	232 (0.2)	0.5395
Live birth	4843 (5.0)	6765 (7.0)	<0.0001

Gn, gonadotropin; **GnRH**, gonadotropin-releasing hormone; **hCG**, human chorionic gonadotropin; **MS**, multiple sclerosis.

LIMITATIONS

- Claims data are not specifically collected for research purposes, and diagnostic and drug-use information are not always validated; as such, there can be missing information that limits the inferences that can be made from the data.
- The ICD-9-CM code for systemic MS does not distinguish between different MS types (e.g. primary progressive, relapsing–remitting, and secondary progressive MS).
- US administrative claims databases provide information on individuals with health insurance administered by regional health plans in the US, and the results may not be generalizable to individuals who self-pay or those without employer-sponsored commercial health insurance.

CONCLUSIONS

- **Compared with women without MS, women with MS were more likely to have a diagnosis of infertility, less likely to use infertility treatments, and less likely to have a live birth.**
- **This exploratory analysis should be interpreted with caution as it is only representative of a commercial population sample and further research is warranted.**

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