Reproductive history of the Danish multiple sclerosis population
A register-based study
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Abstract

**Background:** A diagnosis of multiple sclerosis (MS) may impact the choice of parenthood.

**Objective:** To investigate the number of live births, abortions and ectopic pregnancies among persons with MS.

**Methods:** From the Danish Multiple Sclerosis Registry, we extracted data from all persons diagnosed with MS from 1960–1996 and matched each MS person with four reference persons. We used a negative binomial regression model for the live births and Poisson regression model for abortions and ectopic pregnancies. The total fertility rate (TFR) during 1960–2016 and the annual number of live births in the MS population were analysed.

**Results:** Persons with MS had fewer children than reference persons. Fewer women with MS had elective abortions after diagnosis (incidence rate ratio [IRR] 0.88; 95% CI 0.78–1.00) than reference persons. There was no difference regarding the number of elective abortions, spontaneous abortions or ectopic pregnancies after onset. The TFR was lower for women with MS than for reference persons, and the number of annual live births by MS persons increased during 1960–2016.

**Conclusion:** MS seems to considerably impact reproductive choices, especially after clinical diagnosis, resulting in the MS population having fewer children than the general population.
Introduction

A diagnosis of multiple sclerosis (MS) may impact the choice of parenthood for persons with MS. MS is a chronic demyelinating disease of the central nervous system.\(^1\) The average clinical onset of MS is 30 years of age, and the female to male ratio has increased to more than 2:1 in recent decades.\(^2\) Therefore, the majority of persons with MS are women in their reproductive years, with many having conceived children before their MS diagnosis, whereas others start a family afterwards. Family planning is a major life event in any person’s life but even more so for persons with chronic illness because of the possible symptoms and disabilities that can impact the life of persons with MS, the partner and their children.\(^3\) From the perspective of the treating neurologist, an added complication is managing the disease-modifying therapies (DMTs) carefully in relation to family planning and the postpartum period.\(^4\)

Before the Pregnancy in MS (PRIMS) study by Confavreux et al. in 1998\(^5\) that showed no long-term adverse effects from pregnancy on the course of MS, women with MS had been advised by physicians not to have children due to the concern of worsening their MS disease course.\(^6\) In a Canadian survey regarding the choice of parenthood after a diagnosis of MS, 72.5% of Canadian persons with MS and 75.2% of American persons with MS responded that they had no preference about having any/more children.\(^7\) This preference was reported even in a time when DMTs were available for the majority of the respondents since the survey was conducted in 2007–2008. The rate of spontaneous abortions and ectopic pregnancies among women with MS seems to be comparable to that of the general population.\(^8\)–\(^10\) There has only been one previous pregnancy study in a nationwide population that originated from Norway and reported 649 live births by 461 women with MS compared to 2.1 million births among 1.0 million women without MS during 1967–2002.\(^11\)

The objectives of this study are to investigate the number of pregnancies and live births among women and men in the Danish MS population. We will compare the total fertility rate (TFR) of women with MS in relation to the general Danish population. Additionally, we will report the annual number of live births
among women and men with MS. Furthermore, we will compare the number of live births for persons with MS and number of elective and spontaneous abortions and ectopic pregnancies for women with MS compared with a matched reference cohort.

Methods

Study design

We conducted a cohort study based on nationwide data from the Danish Multiple Sclerosis Registry. Persons with clinically isolated syndrome (CIS) or confirmed MS constituted the ‘MS cohort’. Randomly selected persons from the general Danish population without MS constituted the ‘reference cohort’ and were matched by sex, year of birth and vital status with persons in the MS cohort. Statistical analyses were conducted separately for women and men.

Study population

MS cohort

From the nationwide population-based Danish Multiple Sclerosis Registry, 22,290 persons in total were retrieved (1,885 with CIS and 20,405 with a confirmed MS diagnosis). The diagnoses were determined by neurologists according to the following diagnostic criteria that was current at the time of diagnosis: Allison & Millar until 1994, Poser until 2004, and McDonald from 2005. Only persons diagnosed between 1960–1996 were included. Follow-up was until 31 December 2016, which allowed at least 20 years of follow-up for all persons.

Reference cohort

The reference cohort without MS was identified through the Danish Civil Registration System. Persons in the reference cohort were selected by matching the individuals of the MS cohort by sex, year of birth, vital status and residence in Denmark in the year that the person with MS was diagnosed. We randomly sampled four reference persons per one individual in the MS cohort. The matched reference persons were assigned the same dates of onset and diagnosis as the matched MS person to provide a date for the
comparison analyses regarding the live birth, abortion and ectopic pregnancy counts.

**MS population**

From the 22,290 persons in the MS cohort, we selected persons who were alive, diagnosed with MS and living in Denmark and between 15–49 years of age in the investigation year to report the TFR and the annual number of live births during 1960–2016.

**Data sources**

*The Danish Multiple Sclerosis Registry* was established in 1956 and is nationwide and population-based. All prevalent MS cases in 1948 and incident cases with onset after 1947 are included. The Danish Multiple Sclerosis Registry is validated annually by linking patients to the incidence cases in the National Patient Register. The cohorts were categorized into four age groups by age at diagnosis: <25; 25–34; 35–44; and >44 years to use as covariates.

*The Danish Civil Registration System* was established in 1968 and contains all Danish residents by assigning a unique identification number to each person to link to the registers. This number is used throughout life by all public authorities from birth and through education, employment and death.

*The Population Statistics Register* was established in 1971 and contains information on births, deaths, marriages, registered partnerships, migrations and adoptions. The cohorts were categorized by year of birth into three categories: 1896–1939; 1940–1949; and 1950–1986; their number of children before diagnosis were categorized into three groups: 0, 1, and 2 or more children to use as covariates.

*The Population’s Education Register* was established in 1981 and contains information on all educational achievements from preschool up to the PhD level. The register has a high validity and coverage (96.4% in 2008). We had access to the educational data from 1981–2016. We categorized the highest completed educational levels of the cohorts into four categories: primary school; secondary school; vocational
educational training, short or medium higher education, bachelor (BA); and long higher education, PhD to use as covariates.

*The Register of Legally Induced Abortions* was established in 1973 and contains information on all abortions induced legally according to Danish abortion law. It has been legal since October 1973 to perform abortions before the end of the 12th week of gestation in Denmark. We had access to data from 1975–2016. We determined the induced abortions as O04, O05 and O06 based on ICD-10 (the International Statistical Classification of Diseases and Related Health Problems). We investigated the number of abortions after a MS diagnosis because knowledge of a chronic illness might influence the choice for elective abortion.

*The Danish National Patient Register* was established in 1977 and contains the activities in all the Danish public and private hospitals regarding diagnoses, treatment, dates of admittance and discharge, and demographics of the patients. We had access to data concerning spontaneous abortions and ectopic pregnancies from 1979–2016.

The number of persons in the analyses depended on the time frames of the registers.

**Ethics**

Statistics Denmark encrypted the data from the registers and stored the linked datasets and analyses on their secure, logged servers. We linked the data and performed the statistical analyses by using the encrypted individual-level identification numbers.

The Danish Data Protection Agency approved the study for research and statistical usage [30-1141 and RH-2017-32 05248]. According to Danish law, ethical committee approval was not necessary since we had no biomedical sampling or patient involvement.

**Statistical methods**
Descriptive statistics were applied to give an overview of the baseline characteristics of the two matched cohorts used in the comparison analyses.

For the two cohorts, the number of live births was analysed using a negative binomial regression model. In the analyses of live births before onset or diagnosis, the persons were followed from 15 years of age until onset or diagnosis. In the analyses of live births after onset or diagnosis, the persons were followed from onset or diagnosis until follow-up. Women and men were analysed separately.

The association between the MS cohort and number of abortions and ectopic pregnancies relative to those of the reference cohort were analysed using a Poisson regression model. For elective abortions, the persons were followed from onset or diagnosis until follow-up. For spontaneous abortions and ectopic pregnancies, the persons were followed from onset until follow-up. Abortions and ectopic pregnancies were only analysed for women.

The negative binomial and Poisson regression analyses were reported with incidence rate ratios (IRRs), 95% confidence intervals (CIs) and p-values both unadjusted and adjusted by year of birth, educational level, age at onset or diagnosis and number of children before onset or diagnosis. The cohort data were censored at emigrated date, date of death, 50th birthday or end of follow-up (31 December 2016).

The TFRs of women in the MS population and women in the general Danish population were reported from 1960 to 2016. The TFR is the average number of children 1000 women would have if the annual age-specific rates remained constant throughout the childbearing years (15-49 years of age). The TFR was calculated for women from 15–49 years of age who were alive in the analysed year.

For women with MS, the annual number of live births after diagnosis were reported from 1960–2016. The same analysis was conducted for men with MS.
All statistical tests were performed using SAS software version 9.4.

Results

Cohort comparisons of live births, abortions and ectopic pregnancies

We included 9,385 persons in the MS cohort (5,789 women) and 37,536 reference persons without MS (23,152 women) in the cohort analyses (Figure 1). The female to male ratio was 1.6:1 (Table 1). A higher percentage of persons with MS died than that of reference persons (52.3% vs 32.6%), which is to be expected when the median year of birth was 1945 (range 1896–1986).21 The median age at onset was 33 years (range 2–74) and, at diagnosis, was 38 years (range 5–82).

[Please insert Figure 1 + Legend]
[Please insert Table 1]

Women with MS had fewer children (IRR 0.63; 95% CI 0.60–0.66, p<.0001) than the matched reference women, and men with MS (IRR 0.69; 95% CI 0.65–0.74, p<.0001) had fewer children than the reference men, both after onset and after diagnosis (Table 2). Additionally, only women with MS had fewer children before diagnosis and onset than the reference women (Table 2). The difference between the MS cohort and the reference cohort increased from onset to diagnosis, resulting in fewer children for the MS cohort after diagnosis than after onset.

[Please insert Table 2]

We conducted two sensitivity analyses regarding births (Supplementary file 1). First we compare women with MS ever treated with DMT with never treated women with MS. When we adjust for age and year of birth, we obtain a significant difference in the IRR for women ever treated with DMT having fewer children than the non-treated MS women.
Secondly, women with an EDSS of either 2–3 or EDSS >3 have lower fertility compared with women with an EDSS <2.

For abortions and ectopic pregnancies, we only included women from the two cohorts (Table 3). Fewer women with MS had elective abortions after diagnosis (IRR 0.88; 95% CI 0.78–1.00, \( p=0.0497 \)) than reference women. There were no differences regarding elective abortions (IRR 0.92; 95% CI 0.82–1.03, \( p=0.1443 \)), spontaneous abortions (IRR 1.06; 95% CI 0.83–1.35, \( p=0.6212 \)) or ectopic pregnancies (IRR 1.18; 95% CI 0.92–1.53, \( p=0.1899 \)) after onset.

[Please insert Table 3]

**Total fertility rate (TFR)**

The TFR was consistently lower for women with MS than for the general Danish female population from 1960 to 2016 (Figure 2). The numbers supporting Figure 2 are available online (Supplementary file 2). The TFR of the women with MS followed the general population’s TFR, albeit consistently with a lower rate.

[Please insert Figure 2 + Legend]

**Annual live births after diagnosis of MS persons**

Generally, for women and men with MS, the number of annual live births after diagnosis increased from 2000–2016 along with the percentage of the MS population that chooses to have more children (Figure 3). The numbers supporting Figure 3 are available online (Supplementary file 3).

[Please insert Figure 3 + Legend]

**Discussion**

In our nationwide population-based cohort study, we found that women with MS had consistently lower
TFRs than women without MS and that both women and men with MS had fewer live births after diagnosis than the reference cohort. These two findings strengthen each other. Women with MS had slightly fewer elective abortions after diagnosis than reference women; however, there was no difference in the number of elective abortions after onset. Likewise, the rate of spontaneous abortions and ectopic pregnancies were similar between women with MS and reference women.

The reported TFRs of women with MS and the general population were calculated using nationwide, population-based register data. The TFR is an often-used demographic reproductive measure that gives an interpreted absolute number of births for a given woman throughout her reproductive life course. Our findings of a lower TFR and fewer children born after a diagnosis to persons with MS than those of reference persons are supported by previous studies. In a survey study from Italy with 303 MS patients and 500 controls, the fertility rate was 0.43 in women with MS and 1.45 in controls. People might plan their family situation differently after being diagnosed with MS since their degree of disability, fatigue, partnership status or economic circumstances can all impact the decision to start or expand a family.

For women with MS, the majority of childbirths occurred before diagnosis, so this could have influenced the decision to not have any more children after diagnosis because the persons with MS already deemed their family complete.

At follow-up, 2,404 persons with MS (25.6%) versus 7,475 reference persons (19.9%) were childless (Table 1). In a survey using data from Canada and the US, about two-thirds of the women and men with MS did not have children following diagnosis, and 34.5% of the men and women attributed this choice to MS-related concerns regarding parenting, burdening their partner or hereditary risk. In a French observational study with 115 women with MS, 20 women (17.4%) had chosen to remain childless. In an Italian survey study, 67 women with MS (22%) were childless compared to 66 control women (13%); of the women with MS, 16% attributed the choice of remaining childless to MS, e.g., worsening disabilities, hereditary risk, DMT pause or discouragement by their physician.
Fewer women with MS had elective abortions after diagnosis than reference women. One explanation might be that women with MS are prescribed DMT as treatment, and the DMT must be discontinued before pregnancy. However, because women with MS are in the habit and mindset of having to remember their DMT, it could be easier to remember taking contraceptives, which can diminish the risk of unplanned pregnancies.

We found similar rates regarding spontaneous abortions and ectopic pregnancies when comparing women with MS with a reference group of women without MS. These findings are supported by other studies, even when the mother and foetus might have been exposed to DMT, e.g., interferon-beta-1b\textsuperscript{24}, natalizumab\textsuperscript{25}, teriflunomide\textsuperscript{26} or even mitoxantrone.\textsuperscript{9} Notably, if the woman had been exposed to fingolimod,\textsuperscript{27} she had a slightly higher risk of spontaneous abortions than the general population. Thus, MS by itself should not predispose women to a higher rate of spontaneous abortions and ectopic pregnancies.\textsuperscript{23,28}

Previous studies using data from The Danish Multiple Sclerosis Registry have taken different approaches regarding reproduction and focused on reproductive history and the risk of developing MS. A case-control study by Magyari et al. reported that women with MS have fewer births before clinical onset compared with matched controls without MS, and childbirth within five years of clinical onset significantly reduced the risk of MS in women.\textsuperscript{29} A study by Nielsen et al. similarly reported that having a child reduced the risk of MS in both women and men.\textsuperscript{30}

There has only been one other nationwide register-based study stemming from Norway that focused on pregnancy and delivery among women with MS, and it found an increase in planned caesarean delivery and a need for intervention during vaginal birth and neonates who were small for their gestational age.\textsuperscript{11} Another study found that women with MS have slightly higher rates of caesarean deliveries and labour induction than reference women.\textsuperscript{31} In contrast, other studies have found no differences in the risk of caesarean delivery, instrumental delivery or small neonates for their gestational age.\textsuperscript{22,32}
Previous studies have mainly focused on pregnancy outcomes related to a specific DMT, with some exceptions; a claims study by Houtchens et al. found that women with MS had an increased rate of pregnancy compared with women without MS. In contrast, we analysed the TFR, number of live births and rates of abortions and ectopic pregnancies using data from nationwide population-based registries with high validity and completeness. Some of the strengths of register-based studies are that the data are not dependent on memory or willingness to participate because all the data are mandatorily registered, thus avoiding selection and recall bias. Additionally, the inclusion period for the TFR from 1960–2016 provides a long time frame for real world observation, and the outcome supports the comparison analysis of live births, thus strengthening the findings.

The aim of the article was to describe the TFR of the women with MS as far back as possible in comparison with the TFR of the general population. Despite continuous data collection throughout the last 60 years, we only have clinical characteristics of the MS population since 1996. We focused on the TFR and childbirth rates in this study to provide a longitudinal perspective that spans decades.

We adjusted for educational level as a measure of socioeconomic position since a previous Danish study showed that persons with MS have similar educational levels as persons without MS. Furthermore, another study reported comparable income levels between employed persons with MS and reference persons, although the risk of unemployment increased significantly during the disease course. Therefore, we chose to adjust for educational level instead of income.

In conclusion, women and men with MS are often of reproductive age when the onset of MS occurs, and children are a natural part of this life period. Having MS seems to considerably impact reproductive choices and results in fewer children throughout the reproductive years, especially after diagnosis. The risk of being childless or not having additional children after diagnosis was increased by the lack of a stable partner, declining socioeconomic circumstances and MS-related issues. Family planning should continue to be an
important topic in clinical practice.

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**Declaration of conflicting interests**

JY Moberg has served on the scientific advisory board for Biogen, received speaker honoraria from Biogen, Sanofi Genzyme and Teva Denmark, and received support for congress participation from Biogen, Merck, Sanofi Genzyme and Teva Denmark. B Laursen has nothing to disclose. LC Thygesen has nothing to disclose. M Magyari has served on the scientific advisory boards for Biogen and Teva Denmark, received speaker honoraria from Biogen, Merck, Novartis and Teva Denmark and received support for congress participation from Biogen, Merck, Novartis, Roche, Teva Denmark and Sanofi Genzyme.

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