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Male factor infertility and risk of multiple sclerosis: A register-based cohort study

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Abstract

Background: Gender, possibly due to the influence of gonadal hormones, is presumed to play a role in the pathogenesis of multiple sclerosis (MS), but no studies have evaluated whether male infertility is associated with MS.

Objective: To study the association between male factor infertility and prevalent as well as incident MS.

Method: Our cohort was established by linkage of the Danish National in vitro fertilization (IVF) registry to The Danish Multiple Sclerosis Registry and consisted of 51,063 men whose partners had undergone fertility treatment in all public and private fertility clinics in Denmark between 1994 and 2015.

Results: With a median age of 34 years at baseline, 24,011 men were diagnosed with male factor infertility and 27,052 did not have male factor infertility and made up the reference group. Men diagnosed with male factor infertility had a higher risk of prevalent (odds ratio (OR) = 1.61, 95% confidence interval (95% CI) 1.04–2.51) and incident MS (hazard ratio (HR) = 1.28, 95% CI 0.76–2.17) when compared to the reference group.

Conclusion: This nationwide cohort study has shown, for the first time, an association between male infertility and MS which may be due to underlying common etiologies such as hypogonadism, shared genetics, or a joint autoimmune component.

Keywords: Male infertility, gender, multiple sclerosis, fertility, semen quality, epidemiology

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Introduction

Multiple sclerosis (MS) is a chronic, autoimmune disease characterized by axonal demyelination which may lead to varying degrees of neurological symptoms and disability.[1] The disease is more common in the Western world with prevalent estimates of 150/100,000 implying both genetic and environmental causes, although the etiology remains unknown.[2] Differences in the risk profiles among women and men suggest that gender, possibly due to different levels of sex hormones, plays a role in both etiology and disease course. For example, pregnancy is known to play a protective role for relapses, but the relapse rate tends to increase shortly after giving birth.[3] Moreover, MS in men is often associated with later onset, greater progression, and a worse prognosis especially due to increased brain atrophy and cognitive impairment.[4,5]

Although the relationship between female reproductive factors and MS has been widely investigated, including the increased risk of relapses among women after fertility treatment,[6] less attention has been paid to the association between male reproductive health and MS risk. A recent study showed that men with MS have lower levels of endogenous testosterone, a potential marker for male infertility, suggesting a common etiology may exist.[7] Furthermore, the onset of MS generally occurs when a man's own testosterone levels tend to decline and lower levels have been associated with higher disability.[8] This might be related to the anti-inflammatory effect of testosterone which has been shown to play a neuroprotective role in both animal[9] and one clinical study.[10] It has also been suggested that men with MS have poorer semen quality, but whether these findings are due to an underlying fertility

problem or adverse effects related to treatment is unknown.[11] Nonetheless, one Danish study suggested that the risk of MS seems to decrease with the number of children fathered,[12] but another study did not confirm these findings[13] leaving the association uncertain.

Male infertility has been linked to an increased risk of certain cancers, chronic diseases, and mortality, but the risk of autoimmune diseases such as MS has not been previously been explored.[14] The aim of this study was to investigate the association between male factor infertility and prevalent as well as incident MS in a nationwide cohort of men identified from the Danish IVF register.

Materials and methods

Setting

In Denmark, fertility treatment is covered by the public healthcare system if the woman is under 40 years of age and if the couple has no common children or for single women who are childless. In the private sector, fertility treatments are allowed until the woman's 45th birthday. About 50% of all treatments are performed through public healthcare. The IVF clinics in Denmark perform a high volume of semen analyses used for fertility evaluations and sperm preparations for assisted reproductive technology (ART) treatment. A semen sample must be provided as part of the male evaluation before initiation of treatment. It is generally accepted that a man must provide a second semen sample if the first analysis is subnormal. Thus, any diagnosis of reduced semen quality is generally based on two consecutive tests.

Study population

We defined a historic cohort of all men identified from the Danish National IVF register from 1 January 1994 to 31 December 2015. Using the unique identification numbers held by all Danish citizens, linkages were made to The Danish Multiple Sclerosis Registry, which includes all persons diagnosed with MS in Denmark. Data regarding date of death, emigration, or disappearance were obtained through Statistics Denmark. The study was approved by the Danish Data Protection Agency J. nr: BFH-2015-091. According to the Danish legislation, register-based studies do not require ethical approval as these studies do not involve direct contact to individuals.

Information regarding male factor infertility

The Danish National IVF registry was established in 1994 and includes data on all men whose partner has undergone fertility treatment, including whether the reason for infertility was due to male, female, mixed, or unexplained infertility.[15] The register was updated in 2006, which resulted in a number of changes including a more detailed documentation of male factor infertility with the *underlying cause* only being available from the new registration period. Hence, from 1994 to 2005, "male factor" was recoded as either "yes" or "no" with no missing values. We have previously described how male factor was defined from 2006 and onwards with the use of International Statistical Classification of Diseases and Related Health Problems (10th revision; ICD-10) codes (e.g. azoospermia and oligospermia).[16] The variable "male factor = no" was generated from men with normal semen quality or those sterilized and made up the reference group. Men with fictive national identification numbers, men from Greenland, and those with an unknown fertility diagnosis were excluded.

Diagnosis of MS

The Danish Multiple Sclerosis Registry is the oldest population-based MS register in the world. It was established in 1956 and consists of all incident persons with onset of MS after 1947. The Danish Multiple Sclerosis Registry due to its high completeness has continuously monitored incidence, prevalence, and survival of MS in Denmark since 1948.[17] The register includes information on Danish MS patients from all departments of neurology, practicing neurologists, MS rehabilitation centers, death certificates, and (since 1977) the Danish Hospital Discharge Register.[18] As the date of MS diagnosis was only recorded by calendar year, we defined the date of diagnosis as 1 July in the same year of diagnosis. None of the identified MS cases died or emigrated in the same year as the diagnosis.

Covariates/confounders

Age was available from the IVF register and included as a potential confounder due to the known effects of age on both fertility and MS. Information regarding highest level of education was obtained from Statistics Denmark and was used as a proxy for lifestyle factors.

Statistical analysis

First, we used logistic regression to calculate the odds ratio with corresponding 95% confidence intervals (95% CI) for prevalent/existing MS. Second, we used Cox regression to calculate the hazard ratio (HR) of MS during follow-up. Both crude and confounder

adjusted risk estimates are reported. For both the cross-sectional and the survival analysis, we analyzed data for (a) the entire IVF registration period (1994–2015), (b) the first IVF registration period (1994–2005), and (c) the second IVF period (2006–2015). Stratified analyses were done to account for differences in reporting of male factor infertility. In the Cox proportional hazards model, the HR of MS was calculated with age as the underlying time scale ensuring that risk estimates were based on individuals at exactly the same age.[19] The men were considered at risk from age of inclusion into the cohort and were followed until the age of MS (event), death, emigration, disappearance, or end of follow-up on 31 December 2015, whichever came first. All analyses were carried out using SAS (version 9.2; SAS Institute, Cary, NC).

Results

In our cohort of 51,063 men, 47% were diagnosed with male factor infertility while 53% were categorized as non-male factor and made up the reference group. Male factor infertility was more prevalent among men identified from the second registration period in comparison to the first IVF registration period (50% vs 40%), respectively. The median age at baseline for those with male factor infertility and the reference group was similar (33.9 vs 33.8 years). Overall, the most commonly reported highest level of education was skilled trade, followed by higher university and a bachelor degree for both men with male factor infertility and the reference group. Among those with male factor infertility, oligospermia 12,784 (35%) was the most prevalent cause followed by other causes/unspecified infertility 3599 (10%) (Table 1).

A total of 49 prevalent MS cases were identified among those with male factor infertility and 36 cases among the reference group. Overall, men with male factor infertility were more likely to have MS compared to the reference group (OR = 1.61; 95% CI 1.04–2.51) (Table 2). The distribution of MS cases differed between the two registration periods with more cases identified among those with male factor infertility from the second registration period. The increased risk persisted among men with male factor infertility identified from the second IVF register (OR = 1.67; 95% CI 1.01–2.84), although not as strongly among those identified from the first IVF register (OR = 1.38; 95% CI 0.57–3.28).

During follow-up, 29 cases of MS were identified among those with male factor infertility and 27 cases among the reference group (Table 3). In both crude and adjusted analyses, men with male factor infertility had a higher risk of developing MS during follow-up compared to the reference group (HR = 1.28; 95% CI 0.76–2.17). However, analyses stratified for IVF registration period were only suggestive of increased MS risks with HRs of 1.08 (95% CI 0.52–2.25) and 1.64 (95% CI 0.73–3.70) for the first and second period, respectively.

Discussion

In our study of more than 50,000 men identified from the Danish National IVF register 1994–2015, we found male factor infertility to be associated with an increased risk of prevalent MS. When the men were followed over time, there still appeared to be an increased risk of incident disease. To our knowledge this study is the first to assess the risk of MS in the years following a diagnosis of reduced male fertility.

There is no evidence to support that male factor infertility *in itself* directly causes MS. We hypothesize that the association, both cross-sectional and longitudinal, may be due to common underlying etiologies, including hypogonadism, genetic factors, or an autoimmune component, which may lead to both male infertility and MS. The observed stronger association between male infertility and prevalent MS than incident MS may be due to the timing of the two diagnoses as the diagnosis of MS may appear before the men wish to start a family and realize they need help to do so. Hypogonadism, in particular, has been associated with worse clinical outcomes, and a recent English study found testicular hypofunction (a potential marker for hypogonadism) to be a risk factor for MS.[7] Testosterone may play a neuroprotective/anti-inflammatory role according to animal studies.[9,20] One animal model study found lower endogenous levels of testosterone among mice with MS,[21] and therapeutic testosterone treatment has been shown viable in restoring hippocampal function which could potentially have an effect on cognitive impairment among patients with MS.[22] Similar findings have also been shown in a human study which found testosterone treatment to significantly increase gray matter in the frontal cortex supporting the potential of testosterone treatment to stall neurodegeneration associated with MS.[10] Also, as MS is more common in women, it is evident that gender is an independent risk factor for MS, further suggesting that gonadal hormones play a role, but the particular influence remains unknown. A large register-based study found that men who had undergone male-to-female transgenderism had a sixfold higher risk of a subsequent MS risk further supporting the role of hypogonadism/feminizing

Table 1. Baseline characteristics of the cohort.

	Male factor infertility[a]		Reference group[b]	
	N (%)	Median (5th–95th percentile)	*N* (%)	Median (5th–95th percentile)
All men (1994–2015) (n = 51,063, 100%)				
N	24,011 (47.0)			27,052 (53.0)
Age at baseline (years)		33.9 (26.2–46.0)		33.8 (26.2–45.3)
Follow-up time (years)		7.4 (0.66–17.2)		6.15 (0.67–19.7)
Highest level of education				
Primary school	3418 (14.8)		3796 (14.6)	
High school	1761 (7.61)		1884 (7.3)	
Skilled trade	10,900 (47.1)		12,568 (48.7)	
Bachelor degree	3552 (15.3)		3950 (15.2)	
Higher University	3515 (15.2)		3754 (14.5)	
Men included in IVF register (1994–2005) (n = 14,439, 28.3%)				
N	5724 (39.6)		8715 (60.4)	
Age at baseline (years)		33.8 (26.8–45.4)		33.8 (27.2–44.0)
Follow-up time (years)		14.1 (10.2–9.9)		15.6 (10.3–21.1)
Highest level of education				
Primary school	944 (16.8)		1449(16.9)	
High school	298 (7.1)		606 (7.1)	
Skilled trade	2867 (50.9)		4266 (49.9)	
Bachelor degree	783 (13.9)		1229 (14.4)	
Higher University	636 (11.3)		1001 (11.7)	
Men included in IVF register (2006–2015) (n = 36,624, 71.7%)[c]				
N	18,287 (49.9)		18,337 (50.1)	
Age at baseline (years)		34.0 (25.1–45.2)		33.7 (25.8–45.8)
Follow-up time (years)		5.8 (0.54–9.91)		4.64 (0.39–9.39)
Type of male infertility				
Aspermia	165 (0.45)			
Azoospermia	1739 (4.7)			
Oligospermia	12,784 (34.9)			
Other causes/unspecified	3599 (9.8)			
Highest level of education				
Primary school	2474 (14.1)		2347 (13.5)	
High school	1363 (7.8)		1278 (7.34)	
Skilled trade	8033 (45.9)		8302 (47.7)	
Bachelor degree	2769 (15.8)		2721 (15.6)	
Higher University	2879 (16.4)		2753(15.8)	

IVF: in vitro fertilization.
[a]Includes men with "male factor = yes" identified from the first IVF register and men classified with male factor infertility based on following ICD-10 codes: N469A, N469B, N469C, N469D, N469W, N469X, and N974 (if the man was not sterilized) from the second IVF register.
[b]Includes men with "male factor = no" identified from the first IVF register and men with either normal semen quality or those vasectomized identified from the second IVF register.
[c]Registration in the Danish IVF registry was updated in 2006 from manual to electronic system with a more detailed documentation in the newer years.

hormones on the MS risk in men.[23] Also, a cross-sectional study including subfertile men found low testosterone levels, without the presence of systemic disease, to be associated with elevated inflammatory markers, which could potentially be linked to later onset of inflammatory disease, such as MS.[24] These findings are further supported by a recent cohort study[25] which found significantly higher levels of

Table 2. The association between male factor infertility and prevalent multiple sclerosis.

	Men at risk (*N*)	Cases, *n*	Crude, OR (95% CI)	Adjusted model,[a] OR (95% CI)
Entire IVF register (1994–2015)				
Reference	27,161	36	1.00	1.00
Male factor infertility	24,128	49	1.53 (1.00–2.37)	1.61 (1.04–2.51)
First IVF register (1994–2005)				
Reference	8731	11	1.00	1.00
Male factor infertility	5735	10	1.38 (0.57–3.29)	1.38 (0.57–3.27)
Second IVF register (2006–2015)				
Reference	18,430	25	1.00	1.00
Male factor infertility	18,393	39	1.56 (0.95–2.62)	1.67 (1.00–2.84)

OR: odds ratio; CI: confidence interval; IVF: in vitro fertilization.
[a]Adjusted for highest educational level (indicator: primary school/high school/skilled trade/bachelor/university) and age.

Table 3. The association between male factor infertility and incident risk of multiple sclerosis.

	Men at risk (*N*)	Cases, *n*	Crude,[a,b] Hazard ratios (95% CI)	Adjusted model,[a,b] Hazard ratios (95% CI)
Entire IVF register (1994–2015)				
Reference	27,052	27	1.00	1.00
Male factor infertility	24,011	29	1.28 (0.76–2.17)	1.28 (0.76–2.17)
First IVF register (1994–2005)				
Reference	8715	18	1.00	1.00
Male factor infertility	5724	12	1.08 (0.52–2.25)	1.08 (0.52–2.25)
Second IVF register (2006–2015)				
Reference	18,337	9	1.00	1.00
Male factor infertility	18,287	17	1.64 (0.73–3.70)	1.64 (0.73–3.70)

CI: confidence interval; IVF: in vitro fertilization.
[a]Adjusted for age using it as time scale in the Cox model.
[b]Adjusted for highest educational level (indicator: primary school/high school/skilled trade/bachelor/university).

interleukin-6, a cytokine linked to MS in according to some studies,[26] among infertile men.

A genetic link between male infertility and MS may be possible as one study suggested that parents of MS children had impaired fertility and paternal (but not maternal) age was linked to an increased risk of MS in the offspring, supporting the possibility of germline mutations.[27] This genetic link seems further plausible as a recent study identified genes involved in both male infertility and degenerative diseases.[28] Finally, an autoimmune link may explain the association although this hypothesis is perhaps less likely as autoimmune diseases are more prevalent among women.[29] Nonetheless, MS is considered an autoimmune disease[1] and infertility has been described as having an autoimmune component. Furthermore, a recent case-control found a higher prevalence of both type 1 diabetes and Crohn's disease among men with MS, whereas no association between autoimmune comorbidity and MS was confirmed among the women in the study.[30]

We secondarily hypothesize that the increased risk of especially prevalent MS could reflect that the men present with autonomic dysfunction, including erectile and ejaculatory problems, which may lead them to seek fertility treatment. Alternatively, the reduced semen quality could be either due to an underlying fertility problem or adverse effects related to treatment.[11] The severity of sexual dysfunction depends on the location of the CNS plaques and is not necessarily related to the severity of the disease.[11] Retrograde ejaculation due to neuropathic sequelae associated with MS may be managed by sperm retrieval from the bladder as second line of treatment if pharmacologic treatment is ineffective.[31] For these men, subsequent fertility treatment is necessary to

achieve pregnancy and may partly explain the association between male factor infertility and prevalent MS. These findings are also consistent with cross-sectional studies which have found that young infertile men, already at the time of fertility evaluation, present with more comorbidities than the fertile comparison groups.[14]

Importantly, some studies have found higher rates of childlessness among men and women with MS, but whether these findings are due to reduced fertility or long-standing illness is unknown as the desire to have a child is likely influenced by disease severity.[12,32] Generally, studies relating male infertility to MS are scarce with the main focus so far being on the biological role of pregnancy and effects related to hormonal stimulation among women in fertility treatment. Nonetheless, in our cohort, the baseline prevalence of MS was 167/100,000, which is considerably higher than the national prevalence among Danish men which has previously been estimated to be 107/100,000.[33]

The major strength of this study is its size and ability for the long-term follow-up using national health registers. The MS data were obtained from The Danish Multiple Sclerosis Registry where all included cases are thoroughly evaluated by experienced neurologists. The register has previously been validated with a diagnostic validity of 94%.[18] Also, as our findings were based on unexposed men of the same cohort (an internal reference group), the risk of selection bias is limited as all the men are expected to be similar with respect to other risk factors which could potentially influence the outcome. This is especially important as previous studies have found that couples initiating fertility treatment differ from the general population with regard to health and socio-economic position.[34] In addition, as fertility treatment is covered by the Danish healthcare system for couples where the woman is below 40 years with no common children, we were able to include men from different socio-economic backgrounds, which is relevant as MS has been linked to unemployment and early pension.[35] Our study does also have limitations, some of which have been previously been reported among men identified from the Danish IVF register.[16] First, we relied on the assumption that our reference group men *did indeed* have "normal fertility" although we acknowledge that they still belong to infertile couples and their reproductive capacity may still be reduced in comparison to men from the general population. The direction of bias introduced by this misclassification would most likely be toward the null. Also, the risk of MS was higher among men identified from the second IVF registration period which may be due to exposure misclassification as the reason for male factor infertility was not available among men included from the first registration period. In general, the first IVF registration period is less valid than the second. Moreover, we had limited information regarding smoking and body mass index (BMI), which are suggested risk factors for both male infertility and MS. However, by adjusting for educational attainment, which is a recommended proxy for socio-economic status (SES) among young adults, and closely associated with risk factors as BMI and smoking, we expect to have accounted for most of this possible confounding. We also acknowledge that the hypothesis of an autoimmune association between male infertility and MS would be supported by analyzing testosterone levels, which we do not have available as these are not routinely measured among men in fertility treatment. Finally, we lacked information regarding prior treatments with immunosuppression which could potentially have confounded our results.

Conclusion

Our findings support an association between male factor infertility and MS which may be due to common underlying etiologies such as shared genetics or hypogonadism. Alternatively, our results could reflect the autonomic effects that MS has on male reproductive health. Future studies should further explore the direct impact of infertility on subsequent MS risk in both men and women in order to better understand the role of gonadal hormones and ultimately prevent MS, which presently has no cure and ultimately may lead to long-term disability.

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Declaration of Conflicting Interests

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