

ORIGINAL ARTICLE

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Increased risk of autoimmune disorders in infertile men: analysis of US claims data

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SUMMARY

Aberrations in reproductive fitness may be a harbinger of medical diseases in men. Existing data suggest that female infertility is associated with autoimmune disorders; however, this has not been examined in men. As immune surveillance and hormonal factors can impact male fertility and autoimmunity, we sought to determine the association between male infertility and incident autoimmune disorders. We analyzed subjects from the Truven Health MarketScan claims database from 2001 to 2008. Infertile men were identified through diagnosis and treatment codes. We examined the most common immune disorders, which were identified by ICD9 diagnosis codes. Men diagnosed with an immune disorder at baseline or within 1 year of follow-up were excluded. Infertile men were compared to vasectomized men (i.e., men who are likely fertile) and to age-matched control (10 : 1) group using Cox regression analysis. A total of 33,077 infertile men (mean age of 33 years), 77,693 vasectomized men (mean age 35), and 330,770 age-matched control men (mean age 33) were assembled with a total follow-up of 1.49 M person-years. Overall, immune disorders were rare in the group with the individual conditions occurring in <0.1% of men. However, infertile men displayed the highest risk of many conditions. Infertile men had a higher risk of developing rheumatoid arthritis compared to both vasectomized men (HR 1.56, 95% CI 1.19–2.05) and age-matched controls (HR 1.29, 95% CI 1.02–1.62). Additionally, this higher risk was seen in general immune disorders (under which systemic lupus erythematosus is categorized) compared to vasectomized men (HR 3.11, 95% CI 2.00–4.86) and age-matched men (HR 2.12, 95% CI 1.52–2.96). This same risk trend was seen in psoriasis, when compared to vasectomized men (HR 1.28, 95% CI 1.09–1.50) and age-matched controls (HR 1.20, 95% CI 1.04–1.37). A similar trend was seen in the analysis comparing infertile men and vasectomized men in developing multiple sclerosis (HR 1.91, 95% CI 1.10–3.31) and Grave's disease (HR 1.46, 95% CI 1.10–1.92), as well as the higher risk of infertile men compared to the age-matched group at developing thyroiditis (HR 1.60, 95% CI 1.02–2.52). The current analysis shows that infertile men have a higher risk of developing certain autoimmune disorders in the years following an infertility evaluation. Specifically, infertile men had higher rates of developing rheumatoid arthritis, multiple sclerosis, psoriasis, thyroiditis, and Grave's disease. Given these findings, further research should focus on confirmation of these associations and elucidation of the pathways between fertility and immunity.

INTRODUCTION/OBJECTIVES

Aberrations in fertility may be a harbinger of other medical diseases. Studies have demonstrated that infertile men or men with impaired semen quality have higher rates of several chronic diseases in the years following an infertility evaluation such as cancer (e.g., testis), cardiovascular disease, and diabetes. (Jacobsen, 2000; Eisenberg, 2015a,b; Walsh, 2009, 2010) Investigations have even demonstrated higher mortality rates in men with lower semen parameters. (Eisenberg, 2014; Jensen, 2009)

While immunologic cases of male fertility have been explored, less is understood about later risks autoimmune diseases among

infertile men. The association between infertility and autoimmune disorders is well established in women. (Balasch, 1996; Geva, 1995; Fisch, 1995) This association was first suggested by Kay *et al.* in 1965 that 'subfertility' was increased prior to disease onset of rheumatoid arthritis in women. (Kay & Bach, 1965) Also, it is well documented that autoimmune disorders are associated with reduced fertility. (Jangir & Jain, 2014; Trokoudes *et al.*, 2006) Several groups have demonstrated endometriosis (an established etiology of female infertility is associated with incident autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis). (Sinaii, 2002; Harris, 2016) Given that immunologic causes of male infertility are common, a

higher incidence of immune disorders among infertile men is plausible. For example, multiple sclerosis has been associated with hypogonadism and impaired semen quality. (Safarinejad, 2008; Pakpoor, 2014)

To date, there have been no studies that have found an association between male infertility and the development of an autoimmune disorder. As immune surveillance and hormonal factors can impact male fertility and autoimmunity, we sought to determine the association between male infertility and incident autoimmune disorders.

MATERIALS AND METHODS

Patients

We analyzed subjects in the Truven Health MarketScan Commercial Claims and Encounters database from 2001 to 2009. The MarketScan claims database is made up of adjudicated and paid insurance claims filed for the care of privately insured individuals with employment-based insurance through a participating employer. MarketScan provides claims data on 77 million covered lives since 1996. The number of individuals represented in the database varies over time, and the more recent years of the data that we used contain more than 30 million covered lives.

We focused on a cohort of likely infertile men and identified by outpatient claims with an infertility diagnosis code (ICD-9 606.0 azoospermia, 606.1 oligospermia, 606.9 male infertility, unspecified, and V26.21 fertility testing) or by the presence on any claim of a procedure code for fertility testing or semen analysis/semen preparation (CPT 89300, 89310, 89320, 89321, 89322, 89325, 89329, 89330, 89331). We recorded the first date on which we observed a relevant diagnosis or procedure code as the index date. Given the variation in infertility coding and reimbursement practices in the United States, we attempted to be as broad as possible with our definition.

A comparison group of men age 18–50 with claims containing a procedure code for a vasectomy (CPT 55250 or 55450) was assembled. This group was assumed to be comprised of fertile men given the over 90% of men utilizing vasectomy are fertile. (Eisenberg, 2009) In addition, vasectomized men have similar demographic and socioeconomic characteristics compared to men seeking care for infertility. (Hotaling, 2015) Men in the vasectomy group were assigned an index date as the earliest date of a claim with a vasectomy procedure code and were required to be enrolled in a plan covered by the database for at least 1 year before and 1 year after the index date.

Additionally, a matched control group based on age and database entry date was identified. We selected in a 10–1 ratio, matched control to infertile men. For these men, follow-up time began at the time of insurance enrollment.

For each man, the number of outpatient visits after the index date was determined based on the presence of claims with CPT codes indicating new and follow-up office visits, consultations or preventive medicine encounters. Medical comorbidities were determined based on ICD-9 codes on any claim and included obesity (278.0) and smoking (305.1, V1582).

Autoimmune disorder diagnoses were identified using diagnosis codes on inpatient and outpatient claims. We evaluated the most common male autoimmune disorders including diffuse diseases of connective tissue (a category which includes

Table 1 Baseline characteristics of the cohort

	All Infertility	Vasectomy	Matched control
<i>n</i>	33,077.00	77,693.00	330,770.00
Age			
Mean (SD)	33.00 (5.92)	34.97 (5.89)	32.98 (5.73)
18–19, <i>n</i> (%)	63 (0.19)	110 (0.14)	686 (0.21)
20–29, <i>n</i> (%)	9952 (30.09)	13,978 (17.99)	97,109 (29.36)
30–39, <i>n</i> (%)	18,256 (55.19)	46,319 (59.62)	187,084 (56.56)
40–50, <i>n</i> (%)	4806 (14.53)	17,286 (22.25)	45,891 (13.87)
Follow-up time (years)			
Mean (SD)	3.09 (1.71)	3.27 (1.80)	3.45 (1.80)
1–2, <i>n</i> (%)	10,922 (33.02)	23,053 (29.67)	96,711 (29.24)
2–3, <i>n</i> (%)	8470 (25.61)	18,959 (24.4)	88,007 (26.61)
3–4, <i>n</i> (%)	5985 (18.09)	14,411 (18.55)	65,851 (19.91)
4+, <i>n</i> (%)	7700 (23.28)	21,270 (27.38)	80,201 (24.25)
Total	102,345.70	254,274.40	142,097.80
Obesity, <i>n</i> (%)	769 (2.32)	1564 (2.01)	6381 (1.93)
Smoking, <i>n</i> (%)	845 (2.55)	2674 (3.44)	10,932 (3.31)
Year of evaluation, <i>n</i> (%)			
2001	1333 (4.03)	3105 (4)	17,735 (5.36)
2002	2119 (6.41)	5804 (7.47)	26,599 (8.04)
2003	2960 (8.95)	7521 (9.68)	35,630 (10.77)
2004	4492 (13.58)	10,607 (13.65)	52,208 (15.78)
2005	4269 (12.91)	10,172 (13.09)	40,315 (12.19)
2006	7176 (21.69)	16,456 (21.18)	80,102 (24.22)
2007	6536 (19.76)	14,481 (18.64)	62,400 (18.87)
2008	4192 (12.67)	9547 (12.29)	15,781 (4.77)
Visits per person year, <i>n</i> (%)			
Mean (SD)	2.30 (2.36)	2.51 (2.22)	1.43 (1.81)
<1	10,226 (30.92)	18,035 (23.21)	167,203 (50.55)
1–2	8420 (25.46)	21,440 (27.6)	74,412 (22.5)
2+	14,431 (43.63)	38,218 (49.19)	89,155 (26.95)

systemic lupus erythematosus (SLE)) (ICD-9 710.x), rheumatoid arthritis and other inflammatory polyarthropathies (714.x), ankylosing spondylitis and other inflammatory spondylopathies (720.x), rheumatism, excluding the back (725.x-729.0), regional enteritis (555.x), ulcerative enterocolitis (556.x), multiple sclerosis (340.x), psoriasis (696.x), Grave's disease (242.x), Hashimoto's thyroiditis (245.2), and myasthenia gravis (358).

Statistical analysis

Men accrued at-risk time beginning 1 year after their index dates until autoimmune disorder diagnosis or the last day of enrollment in a health plan in the MarketScan database. The first year was excluded from analysis because an autoimmune disorder diagnosis in this period was an exclusion criterion. We then compared the risk of developing an autoimmune disorder in infertile men to the risk in the vasectomy cohort and the control cohort using a Cox proportional hazard regression model, adjusting for age, evaluation year, smoking, obesity, the number of annual physician visits, and follow-up time. As a sensitivity analysis men diagnosed with an autoimmune disorder before or within 2 years of the index date (i.e., fertility testing or vasectomy) were excluded, the analyses were repeated. All *p* values were two-sided with *p* < 0.05 considered statistically significant. Analyses were performed using SAS (version 9.3).

RESULTS

A total of 33,077 infertile men (mean age of 33 years), 77,693 vasectomized men (mean age 35), and 330,770 matched control men (mean age 33) were assembled with a total follow-up of 1.49 M person-years (Table 1). Overall, immune disorders were rare in the group with the individual conditions occurring in

Table 2 Cox regression models comparing infertile, vasectomy, and control men for autoimmune disorders

	ICD9	All Infertility		Vasectomy		Matched control		HR (95% CI)	
		n (%)	Events/ 100K person- years	n (%)	Events/100K person-years	n (%)	Events/ 100K person- years	Infertile vs. Vasectomy	Infertile vs. Control
Diseases									
Diffuse diseases of connective tissue	710	30 (0.09)	29.31	65 (0.08)	25.56	270 (0.08)	23.64	1.30 (0.84–2.03)	1.19 (0.81–1.74)
Rheumatoid arthritis and other inflammatory polyarthropathies	714	82 (0.25)	80.12	154 (0.20)	60.56	690 (0.21)	60.42	1.56 (1.19–2.05)	1.29 (1.02–1.62)
Ankylosing spondylitis and other inflammatory spondylopathies	720	95 (0.29)	92.82	237 (0.31)	93.21	920 (0.28)	80.55	1.07 (0.84–1.36)	1.13 (0.91–1.39)
Rheumatism, excluding the back	725, 729.0	6 (0.02)	5.86	28 (0.04)	11.01	120 (0.04)	10.51	0.57 (0.23–1.38)	0.51 (0.22–1.16)
Disorders involving the immune mechanism	279	43 (0.13)	42.01	39 (0.05)		221 (0.07)	19.35	3.11 (2.00–4.85)	2.12 (1.52–2.96)
Crohn's disease	555	38 (0.12)	37.96	86 (0.11)	34.45	384 (0.12)	34.34	1.17 (0.79–1.72)	1.08 (0.77–1.50)
Ulcerative colitis	556	62 (0.19)	61.93	134 (0.18)	53.68	550 (0.17)	49.18	1.22 (0.90–1.66)	1.26 (0.97–1.64)
IBD (Crohn's + Ulcerative colitis)	555 + 556	88 (0.27)	87.90	203 (0.27)	81.33	856 (0.26)	76.55	1.15 (0.89–1.48)	1.14 (0.91–1.41)
Multiple sclerosis	340	22 (0.07)	21.97	32 (0.04)	12.82	206 (0.07)	18.42	1.91 (1.10–3.31)	1.18 (0.76–1.84)
Psoriasis	696	226 (0.70)	225.74	468 (0.61)	187.49	2038 (0.63)	182.24	1.28 (1.09–1.50)	1.20 (1.04–1.37)
Grave's disease	242	78 (0.24)	77.91	148 (0.19)	59.29	813 (0.25)	72.70	1.46 (1.10–1.92)	1.06 (0.84–1.34)
Hashimoto's disease	245.2	22 (0.07)	21.97	44 (0.06)	17.63	148 (0.05)	13.23	1.35 (0.80–2.27)	1.60 (1.02–2.52)
Myasthenia gravis	358	6 (0.02)	5.99	9 (0.01)	3.61	46 (0.01)	4.11	1.74 (0.60–5.00)	1.37 (0.58–3.23)

<0.1% of men. However, infertile men displayed the highest risk of many conditions.

Infertile men had a higher risk of developing rheumatoid arthritis compared to both vasectomized men (HR 1.56, 95% CI 1.19–2.05) and age-matched men (HR 1.29, 95% CI 1.02–1.62). Additionally, this higher risk was seen in general immune disorders (under which systemic lupus erythematosus is categorized) compared to vasectomized men (HR 3.11, 95% CI 2.00–4.86) and age-matched men (HR 2.12, 95% CI 1.52–2.96). This same risk trend was seen in psoriasis, when compared to vasectomized men (HR 1.28, 95% CI 1.09–1.50) and age-matched group (HR 1.20, 95% CI 1.04–1.37). A similar trend was seen in the analysis comparing infertile men and vasectomized men in developing multiple sclerosis (HR 1.91, 95% CI 1.10–3.31) and Grave's disease (HR 1.46, 95% CI 1.10–1.92), as well as the higher risk of infertile men compared to the age-matched group at developing thyroiditis (HR 1.60, 95% CI 1.02–2.52) (Table 2).

Given that the rates of immune disorders differ based on age, we performed a stratified analysis to examine men older or younger than 35 years of age at the time of fertility evaluation. In the younger men in the cohort, infertile men had a significant higher risk of developing ulcerative colitis compared to controls (HR 1.55, 95% CI 1.07–2.24). For the men over age 35, the association with ulcerative colitis was not identified. Among men older than 35, infertile men had a higher risk of psoriasis (HR 1.38, 95% CI 1.09–1.75). For psoriasis, the association did not reach statistical significant in younger men.

We performed a sensitivity analysis to exclude men diagnosed within an autoimmune disorder with 2 years of the index date and the increased risk in developing the above autoimmune disorders persisted. For example, infertile men showed a similar point estimate of higher risk for general immune disorders compared to vasectomized men (HR 1.83, 95% CI 0.86–3.91) and controls (HR 1.48, 95% CI 0.81–2.71). Due to the limited number of events, further time points could not be assessed.

DISCUSSION

The current report identified a higher risk of developing certain autoimmune disorders in the years following an infertility diagnosis or evaluation. Infertile men had a higher risk of developing rheumatoid arthritis, general immune disorders (under which systemic lupus erythematosus is categorized), psoriasis, multiple sclerosis, Grave's disease, and thyroiditis. Among men younger than 35, there was a higher risk of developing ulcerative colitis. To our knowledge, this is the first study to examine the risk of incident autoimmune disorders in infertile men.

While there is substantial evidence in the literature regarding female autoimmune disorders and infertility, the association in men is less certain. Given the sex-based differences in the prevalence of many autoimmune disorders, authors have hypothesized hormone-mediated mechanisms. Indeed, studies have shown that men with multiple sclerosis have impaired testicular function as measured by impaired testosterone levels or sperm counts. (Safarinejad, 2008; Pakpoor, 2014) Inflammatory bowel conditions have also been associated with impaired sperm production, but the etiology (i.e., disease vs. treatment for disease) is uncertain. (Sands, 2015)

The mechanism involved in autoimmune disorders and infertility in man is likely complex and involves interactions between the endocrine, immune, and reproductive systems. Autoimmunity is associated with androgen levels, which is a common hypothesis explaining the sex differences in the incidence of autoimmune disorders (females > males). (Ortona, 2016) This too could be a factor linking male infertility and the development of autoimmune disorders, via hypogonadism. Indeed, infertile men are known to have lower baseline testosterone levels compared to fertile men. (Andersson, 2004) The association between testosterone and autoimmunity was assessed in a trial of transdermal testosterone given to men with multiple sclerosis over a 1-year period. (Sicotte, 2007) In these men, testosterone supplementation helped to slow cognitive decline and brain atrophy, but did not affect the number or volume of

enhancing lesions. Sex differences in responsiveness to vaccination have also been demonstrated. Investigators showed that men with higher testosterone levels had diminished antibody responses to the flu vaccine. (Furman, 2014)

Another potential mechanism is cross-reacting antibodies causing both infertility and autoimmunity as have been found to gonadotropin targets. (Cocco, 2014) Alternatively, it is known that subclinical autoimmunity can precede clinical autoimmune disorders by months to years, and this subclinical autoimmunity can impact female fertility. (Gleicher, 1999) In a similar manner, subclinical autoimmunity may affect men. However, to date, the etiology of an association between infertility and immunity remains elusive.

This study is limited using observational data with the inherent unmeasured confounders among groups. The use of administrative data limits the availability of granular data, such as race/ethnic, demographic, and lifestyle data for each man, which may impact conclusions. The MarketScan database only includes commercially insured individuals, thus may not represent all men (Hotaling, 2012). Indeed, the rates of certain autoimmune disorders were different in the cohort compared to the general population. Infertility was identified by claims data alone. We have previously shown good specificity but the poor sensitivity of claims data to identify infertile men. (Khandwala, 2017) As such, infertile men may also exist in the control group, although likely at a much lower prevalence. For example, rheumatoid arthritis (26.9/100K vs. 60/100K) and psoriasis (93.3/100K vs. 134/100K) were more prevalent in MarketScan compared to other US population studies. (Myasoedova, 2010; Icen, 2009) In contrast, the rates of multiple sclerosis (10/100K vs. 13/100K) were comparable. (Mayr, 2003) Moreover, we did identify higher rates of psoriasis in older men and ulcerative colitis in younger men as would be expected based on common ages of onset. Additionally, the number of cases for some autoimmune disorders was small which decreased the power of the observed results. The current results could have occurred by chance or be specific to the infertile men within the MarketScan database; however, a prior study found no association between many common medical comorbidities such as hypertension, hyperlipidemia, chronic obstructive pulmonary disease, anxiety disorder, and liver disease and male infertility arguing against a systemic bias within MarketScan leading to infertile men at higher risk for comorbidity.

Nevertheless, the current data suggest that infertile men are at an increased risk of certain autoimmune disorders in the years following a fertility evaluation. It is important to note that while this represents an elevated relative risk for infertile men, the absolute risk of developing an immune disease remains low. Future research should focus on confirmation of these associations and elucidation of the pathways between infertility and autoimmunity in men.

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