Reproductive pattern in women with idiopathic inflammatory myopathy – a population-based study

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ABSTRACT

Objective

To examine the reproductive pattern of women with idiopathic inflammatory myopathy (IIM) compared to the general population.

Methods

Population-based, nationwide registers were used to identify offspring of women with IIM and comparators.

Results

Women with IIM in general had similar reproductive pattern as the comparators whereas those diagnosed between 26 and 45 years of age there was an overall trend for fewer children as well as trend for a higher proportion of nulliparity and a lower fertility rate in women with dermatomyositis than their comparators.

Conclusion

Reproductive attention should be paid to patients with IIM diagnosed during childbearing period.

INTRODUCTION

There is an increased interest in the reproductive health of patients with rheumatic diseases. (1) The potential reproductive health issues include reduced sexual libido, sexual disability, sub-fertility/infertility, low fecundity and reduced family size. (1) Though the research attention has particularly been focused on patients with rheumatoid arthritis and systemic lupus erythematosus, (1) a few studies suggest that women of childbearing age with idiopathic inflammatory myopathy (IIM) have reduced ovarian reserve, (2, 3) decreased fertility rate, (4) and increased need of assisted reproductive therapy. (5) Two qualitative studies have also found that patients with IIM have problems with sexual dysfunction. (6, 7) To our knowledge, there are no studies investigating the reproductive pattern in women with IIM using population-based methods. We therefore aim to study the proportion of nulliparity, age at first delivery, fertility rate and inter-delivery interval in women with IIM and women from the general population.

MATERIALS AND METHODS

Registers

The Swedish National Patient Register (NPR) has nationwide data on inpatient care since 1987 and holds data on all outpatient visits in non-primary care since 2001. The overall validity of diagnosis in the NPR ranges from 85% to 95%. (8) The Swedish Multigeneration Register (MGR) was established in 1947 and has parental and offspring information on all individuals born in Sweden since 1932. The coverage of data on offspring is nearly 100%. (9)

Study subjects

In this population-based study, we included all women born in 1932 and onwards, who had a first registration indicating IIM between 2001-2016 and at least one follow-up visit within 1-12 months after the first IIM visit in the NPR. This algorithm has been validated with a positive

predictive value up to 94% and a sensitivity up to 96%. (10) Between 1998 and 2000 we only had data on inpatient care, therefore individuals who were discharged with a diagnosis of IIM from inpatient care during that period were also included. International Classification of Diseases, Tenth Revision (ICD-10) codes used were M33.0, M33.1, M33.2 and M33.9 and only ICD-10 codes registered from the internal medicine, rheumatology, dermatology, neurology or pediatrics clinics were considered. IIM was further categorized into juvenile IIM (M33.0), dermatomyositis (DM, M33.1) and other IIM (M33.2 and M33.9). Polymyositis (PM) was studied with other types of IIM as its code (M33.2) often is used for inclusion body myositis. Whenever a patient with IIM was diagnosed, up to five women without IIM, alive and living in Sweden when the case became a case, were randomly selected from the Total Population Register (TPR) and were matched to the IIM patient on birth year and residential area.

Outcomes and other variable

Data linkage to the MGR via the unique identification number enabled us to identify offspring of the study subjects. Nulliparity was defined as not having any registered children; age at first delivery was the age of mother at the first registered child; fertility rate was defined as the number of children per woman; and inter-delivery interval was defined as the average time period from a prior birth to a subsequent birth. Maternal country of birth was identified using the TPR.

Statistical analyses

Characteristics and outcomes in women with IIM were stratified by age at IIM diagnosis (≤ 25, 26-45 and > 45 years) and compared to the comparators without IIM, overall and by IIM subtypes. Results were presented using means with standard deviations (SDs) and medians with interquartile ranges (IQRs) for continuous variables and frequencies with proportions for

categorical variables. Mann-Whitney U test or Chi-square test with 0.05 α-level of significance was used.

Additional analyses were performed including only women born between 1932 and 1972 whose entire reproductive period (15-45 years old) was covered. Since most women diagnosed with IIM ≤ 25 years of age were born after 1972, the analyses were stratified into either ≤ 45 or > 45 years of age at the time of IIM diagnosis. We used SAS version 9.4 package for all statistical analyses. The regional ethics board approval number was 2017/2000-31. Patient consent was waived as this is a register-based study.

RESULTS

In this study, we included 847 women with IIM and 4202 comparators (Figure 1), most of them born in Nordic countries. Among 847 women with IIM, 236 of them (27.86%) were diagnosed with IIM at ≤ 45 years of age (Table 1).

Overall, the proportion of nulliparity, age at first delivery, fertility rate and inter-delivery interval among women with IIM did not significantly differ from the comparators (Table 2). However, women with IIM diagnosed between 26 and 45 years of age had lower fertility rate than the comparators (medians with IQRs: 2 (1-2) vs 2 (1-3), p=0.08; means with SDs: 1.66 ± 1.11vs 1.86 ± 1.25). In the same age group, women with DM had a fertility rate (median (IQR)/mean (SD)) of 2 (0-2)/1.49 (1.16) children/woman and 26.39% of them were nulliparous, versus 2 (1-2)/1.75 (1.19) children/woman (p=0.09) and 19.50% (p=0.19) in the comparators, respectively. Moreover, women with juvenile IIM and women with IIM diagnosed between 26 and 45 years of age were younger at first delivery than their comparators (medians with IQRs: 23 (19-25) vs 25 (20-26), p=0.07; means with SDs: 22 ± 3 vs 25 ± 3, and medians with IQRs: 26 (22-29) vs 27 (23-31), p=0.04; means with SDs: 26 ± 5 vs 27 ± 5,

respectively). Consistent results were found in the additional analyses (supplementary table 1 and 2).

DISCUSSION

In this study we could not detect any differences in nulliparity, age at first delivery, fertility rate and inter-delivery interval in women with IIM compared to the comparators. A case review reported 12% of nulliparity among 78 patients with DM/PM and found no difference from the general population via indirect comparison with data from previously published literature. (11) However, given that only women with DM diagnosed in mid- to late reproductive age were more likely than the comparators to be childless in our study, the apparent discrepancy between the results in the case review and our study could be explained by the fact that women with DM were analyzed together with all others with IIM in the case review. We also observed a tendency of reduced fertility in women with DM diagnosed between 26 and 45 years of age. A Mexican study interviewing patients with DM/PM found a fertility rate of 4.5 children/woman among 17 patients having children before diagnosis and a fertility rate of 1.7 children/woman in 7 patients delivering after diagnosis, however the differences in study design makes it difficult to compare their results to our findings. (4) Somewhat unanticipated findings of our study were that juvenile IIM patients and women with IIM diagnosed in mid-to late reproductive age entered motherhood earlier than the comparators, which contrasts to the ovarian dysfunction among juvenile IIM patients seen in a Spanish study (12) and the observed low level of anti-Müllerian hormone and low astral follicle count in DM and PM patients. (2, 3) This inconsistency may implicate that the improved treatment regimens in IIM, resulting in lower accumulated doses of corticosteroids, may lead to a less affected reproduction. (1, 13)

There are many factors related to reproduction that could have an impact on fertility in women with IIM. Rider *et al* reported that 3 to 5% of adult patients with IIM had sexual dysfunction,

infertility and irregular menses. (14) A Swedish qualitative study of patients with DM/PM identified sexual disability as one of the most common disabilities reported besides traditional IIM symptoms. (7) The suggested factors associated with affected sexuality in IIM were muscle weakness and pain, (6) use of cyclophosphamide or high-dose corticosteroids (1, 6) and medical advice against pregnancy during active disease status. (1) It could also be that patients with IIM are as likely as the any women to conceive but are involuntarily nulliparous or have reduced family size due to frequent miscarriage. (15) This would be in line with our findings that DM patients diagnosed during childbearing period had tendencies of nulliparity and lower fertility rate.

Being limited to register data, we lacked information on individuals' view on childbearing, occurrence of miscarriage, use of contraception, disease activity, autoantibody profile and medication. This precluded us from further analysis and comprehensive interpretation of this study. However, data ascertained from the NPR and the MGR had long follow-up and high quality, (8, 10) allowing inclusion of a large representative sample of women with IIM and ensuring high ascertainment of data on offspring. Matching women with IIM to the comparators by birth year also helped to minimize the bias of cohort differences in childbearing. Inclusion of women still being of reproductive age might not reflect the absolute fertility rate. However, additional analyses limited to women whose entire reproductive period was covered demonstrated similar results.

To conclude, we observed that the reproductive pattern in women with IIM was overall reassuring compared to the comparators without IIM but patients with DM diagnosed in mid- to late reproductive period showed tendencies of nulliparity and reduced fertility, directing further attention to reproductive health among patients with IIM diagnosed during childbearing age.

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FIGURE LEGEND

Figure 1. The flow chart of study population.

TABLES

Table 1. The characteristics of women with IIM (n=847) and comparators without IIM (n=4202) by age at IIM diagnosis.[a]

	Age at diagnosis ≤ 25				25 < Age at diagnosis ≤ 45				Age at diagnosis > 45			
	IIM		Comparators		IIM		Comparators		IIM		Comparators	
Birth year, mean ± SD years												
	N		N		N		N		N		N	
Overall	80	1996 ± 8	403	1996 ± 8	156	1971 ± 8	777	1971 ± 8	611	1947 ± 10	3022	1947 ± 10
Juvenile IIM	67	1997 ± 7	333	1998 ± 7	-	-	-	-	-	-	-	-
DM	5	1991 ± 5	25	1991 ± 4	72	1972 ± 9	359	1972 ± 8	224	1949 ± 10	1117	1949 ± 10
Other IIM	8	1988 ± 7	40	1988 ± 7	84	1969 ± 8	418	1969 ± 8	387	1946 ± 9	1905	1946 ± 9
Age at IIM diagnosis /matching, mean ± SD years												
Overall	80	12 ± 6	403	12 ± 6	156	37 ± 6	777	37 ± 6	611	62 ± 9	3022	62 ± 9
Juvenile IIM	67	10 ± 4	333	10 ± 4	-	-	-	-	-	-	-	-
DM	5	22 ± 3	25	22 ± 2	72	37 ± 6	359	37 ± 6	224	61 ± 10	1117	61 ± 10
Other IIM	8	22 ± 2	40	22 ± 2	84	37 ± 6	418	37 ± 6	387	63 ± 9	1905	62 ± 9
Born in Nordic countries, n (%)												
Overall	80	73 (91.25)	403	370 (91.81)	156	116 (74.36)	777	629 (80.95)	611	554 (90.67)	3022	2724 (90.14)
Juvenile IIM	67	61 (91.04)	333	308 (92.49)	-	-	-	-	-	-	-	-
DM	5	4 (80.00)	25	23 (92.00)	72	49 (68.06)	359	280 (77.99)	224	197 (87.95)	1117	983 (88.00)
Other IIM	8	8 (100.00)	40	37 (92.50)	84	67 (79.76)	418	349 (83.49)	387	357 (92.25)	1905	1741 (91.39)

a IIM = Idiopathic inflammatory myopathy; SD = Standard deviation; N = number of individual; DM = Dermatomyositis.

TABLES

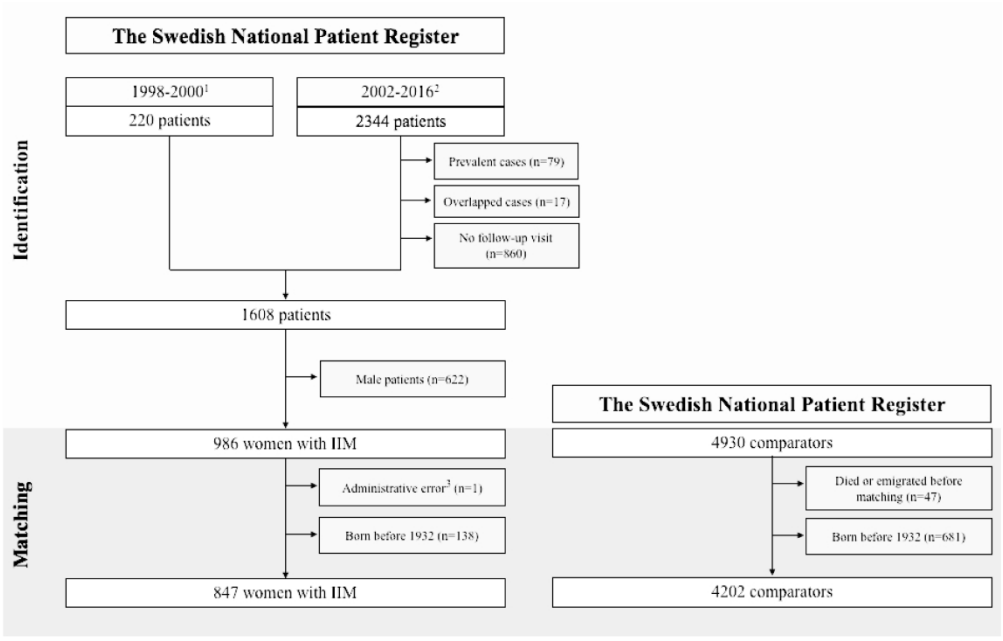
Table 2. The reproductive pattern of women with IIM (n=847) compared to the comparators without IIM (n=4202) by age at IIM diagnosis.[a]

	Age at diagnosis ≤ 25					25 < Age at diagnosis ≤ 45					Age at diagnosis > 45				
	IIM		Comparators		P[b]	IIM		Comparators		P[b]	IIM		Comparators		P[b]
Nulliparity, n (%)															
	N		N			N		N			N		N		
Overall	80	64 (80.00)	403	339 (84.12)	0.37	156	31 (19.87)	777	133 (17.12)	0.41	611	94 (15.38)	3022	403 (13.34)	0.18
Juvenile IIM	67	56 (83.58)	333	291 (87.39)	0.40	-	-	-	-	-	-	-	-	-	-
DM	5	3 (60.00)	25	16 (64.00)	0.87	72	19 (26.39)	359	70 (19.50)	0.19	224	37 (16.52)	1117	158 (14.15)	0.36
Other IIM	8	5 (62.50)	40	28 (70.00)	0.68	84	12 (14.29)	418	63 (15.07)	0.85	387	57 (14.73)	1905	245 (12.86)	0.32
Maternal age at first delivery, median (IQR)															
Overall	16	23 (21-26)	65	24 (22-27)	0.17	125	26 (22-29)	644	27 (23-31)	0.04	517	24 (21-27)	2619	24 (21-28)	0.64
Juvenile IIM	11	23 (19-25)	42	25 (20-26)	0.07	-	-	-	-	-	-	-			-
DM	2	23	9	22 (19-31)	0.91	53	26 (22-30)	289	28 (23-31)	0.36	187	24 (21-28)	959	25 (21-28)	0.54
Other IIM	3	26 (20-30)	12	24 (22-27)	0.94	72	25 (22-29)	355	26 (23-31)	0.07	330	24 (21-27)	1660	24 (21-27)	0.95
Total number of children, n and fertility rate, median (IQR)															
Overall	80	36	403	109		156	259	777	1449		611	1217	3022	6116	
		0 (0-0)		0 (0-0)	0.28		2 (1-2)		2 (1-3)	0.08		2 (1-3)		2 (1-3)	0.89
Juvenile IIM	67	25	333	67		-	-	-	-		-	-	-	-	
		0 (0-0)		0 (0-0)	0.33	-	-	-	-		-	-	-	-	
DM	5	4	25	20		72	107	359	630		224	453	1117	2201	
		0 (0-2)		0 (0-2)	0.95		2 (0-2)		2 (1-2)	0.09		2 (1-3)		2 (1-3)	0.48
Other IIM	8	7	40	20		84	152	418	819		387	764	1905	3915	
		0 (0-2)		0 (0-1)	0.58		2 (1-2)		2 (1-3)	0.43		2 (1-3)		2 (1-3)	0.70
Inter-delivery interval, median (IQR)															

Overall	20	2.00 (1.59-2.58)	42	2.46 (1.75-3.50)	0.16	133	3.00 (2.09-4.83)	778	2.92 (2.00-4.58)	0.45	683	3.25 (2.17-5.08)	3426	3.25 (2.17-4.92)	0.59
Juvenile IIM	14	1.92 (1.59-2.67)	23	3.00 (1.75-3.41)	0.12	-	-	-	-	-	-	-	-	-	-
DM	2	2.29 (2.08-2.49)	11	2.16 (1.25-3.92)	0.92	54	3.00 (2.09-4.41)	330	3.09 (2.00-4.91)	1.00	257	3.25 (2.09-4.83)	1213	3.33 (2.17-4.92)	0.84
Other IIM	4	1.83 (1.08-5.00)	7	2.25 (2.08-5.67)	0.64	79	3.00 (2.00-5.09)	448	2.83 (2.00-4.33)	0.32	426	3.33 (2.17-5.17)	2213	3.24 (2.17-4.92)	0.41

a IIM = Idiopathic inflammatory myopathy; N = number of individual; IQR = Interquartile range; DM = Dermatomyositis.

b *P* from Chi-square test for categorical variable and from Mann-Whitney U test for continuous variable.



[1] A hospitalisation indicating incident IIM.
[2] Diagnosis of incident IIM with at least one follow-up visit within 1-12 months after the first IIM indication.
[3] Potential case of administrative error as this patient had record of follow-up visit during emigration time. However, the five comparators matched to this patient were kept.

Figure 1. The flow chart of study population.

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