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Sexual function and reproduction can be impaired in men with rheumatic diseases: A systematic review

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ABSTRACT

Background: Information about the possible effect of rheumatic diseases on male sexual function and reproduction (sexual health) is scarce and difficult to summarize. Factors known to impair sexual health, such as inflammation, medication use and hypogonadism can be present in a significant proportion of male patients with rheumatic diseases.
Objectives: The objective of our study was to systematically review the literature for the influence of paternal rheumatic disease on sexual health, such as sexual function, reproductive hormones, male fertility, pregnancy and offspring outcomes.
Data sources: English language articles identified through Embase, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Google Scholar and the Clinical trial registries of Europe and the USA published until February 2019.
Study appraisal and synthesis methods: Literature was synthesized in narrative form and in summary tables. Outcomes were categorized as: sexual function, reproductive hormones, fertility and pregnancy and offspring outcomes. Results are presented per category and per disease.
Results: 9735 articles were identified with our search strategy. After removal of duplicates, excluding articles by screening titles and abstracts and assessing eligibility by reading 289 fulltext articles, 87 articles fulfilled the eligibility criteria. All included studies enrolled patients diagnosed with a rheumatic disease and had results at least on one of the outcome categories. Sexual function was the most common category, followed by reproductive hormones, fertility and pregnancy and offspring outcomes. Sexual function is impaired in a high proportion of patients with rheumatic diseases. This was statistically significant in most of the studies where a control group was available. Clinically relevant abnormalities in reproductive hormones were mainly identified in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) and a positive correlation with disease activity were reported. Semen quality in men with rheumatic diseases can be impaired in patients with SLE, SpA, sarcoidosis, BD and MWS. Sperm count and motility were the most common semen quality parameters affected. No negative effect of paternal RA and vasculitis on pregnancy outcomes were reported in 3 studies. No studies reporting the effect of paternal disease on offspring outcomes were identified.
Limitations: Most of the studies included in this review suffer from an inconsistent methodological quality, definitions of outcomes varied in several studies, a wide variety of screening questionnaires and/or diagnostic tools were used and results might only apply to the specific populations that were studied.
Conclusions: This systematic review suggests that sexual health is impaired in men with rheumatic diseases. The degree and extent of sexual health impairment vary per disease. More research is needed to fully

Abbreviations: APS, Antiphospholipid syndrome; AS, Ankylosing spondylitis; BS, Behçet syndrome; CENTRAL, Cochrane Central Register of Controlled Trials; CI, Confidence interval; CYC, Cyclophosphamide; DAS28, Disease activity score (28 joints); DFI, DNA fragmentation index; DHEA, Dehydro-epiandrosterone sulfate; DMARDs, Disease-Modifying Anti-Rheumatic Drugs; ED, Erectile dysfunction; FSH, Follicle stimulating hormone; FMF, Familiar Mediterranean fever; GPA, Granulomatosis with polyangiitis; IIEF, International index of erectile function; IMD, Immune mediated diseases; IU, International units; KS, Klinefelter syndrome; LH, Luteinizing hormone; MWS, Muckle-Wells syndrome; OR, Odds ratio; PsA, Psoriatic arthritis; RA, Rheumatoid arthritis; SD, Sexual dysfunction; SLE, Systematic lupus erythematosus; SLEDAI, Systematic lupus erythematosus disease activity index; SpA, Spondyloarthropathies; SR, Systematic review; SSc, Systemic sclerosis; WHO, World Health Organization

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understand the link between rheumatic diseases and impaired male sexual health. Meanwhile, rheumatologists should be aware of this association and discuss it with their patients.
Implications of key findings: Sexual health of men with rheumatic diseases can be impaired by the disease itself. Especially in men trying to conceive, information on sexual function, reproductive hormones and sperm quality are needed to identify these problems. Treatment resulting in lower disease activity can improve overall sexual health in man with rheumatic diseases and facilitate their journey to fatherhood.
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Clinical case

A 38-year-old man was recently diagnosed with rheumatoid arthritis (RA). During the first follow up appointment he informs his rheumatologist, that he and his wife wish to conceive in the near future. For this reason, they want information about whether RA can affect sexuality and pregnancy outcomes. During the discussion it becomes apparent that the patient is having problems regarding his sexual function; sexual intercourse causes pain and sometimes getting an erection is difficult. He is worried that his RA could interfere with his sexual health and more importantly, his desire to become a father. The rheumatologist discusses treatment strategies that are known to be safe in men with a wish to conceive and promises to come back to him with more information about RA related sexual health outcomes. Thereafter, the rheumatologist discusses with some of his colleagues several questions:

1. Can rheumatic diseases affect male sexual function, reproductive hormones, fertility and pregnancy outcomes? Can disease activity impair male sexual health?
2. Which sexual health problems are common in male patients with rheumatic diseases?
3. In male patients with rheumatic disease, what is the importance of good paternal health for positive pregnancy and offspring outcomes?

Introduction

Rationale

This case described above represents a frequent clinical scenario for rheumatologists around the world. For many years rheumatic diseases have been considered as diseases of women though it is estimated that the overall lifetime risk for developing a rheumatic disease for men is 1 in 20 [1]. Especially in studies on reproductive rheumatology, there is a clear gender bias that has resulted in significant scientific knowledge focused only on the female perspective. Reducing this knowledge gap is important because sexual health and reproduction are as important for men as it is for women.

Sexual health, the state of physical, mental and social well-being in relation to sexuality, has been recognized as an important factor than can have positive or negative effects in an individual's quality of life and the World Health Organization (WHO) states that sexual health problems require specific action for their identification, prevention and treatment. Men diagnosed with rheumatic diseases have specific needs and thus require a health strategy of their own [2,3]. Nonetheless, information regarding this topic is scarce and scattered.

In addition to this, the WHO also considers the need to make informed and responsible choices about reproduction as one of their main sexual health concerns [4]. Human reproduction is a biological process that requires the correct structure and function of several organs and systems in men and women. For men, an adequate testicular function that results in healthy spermatozoa can be considered as one of the most important steps in male reproduction, but many other factors contribute to the success of a spermatozoon fertilizing an ovum, from a delicate balance among hormones secreted in the hypophysis and the testicles (*reproductive hormones*) to spermatogenesis and proper conditions for storage of the mature spermatozoa (*fertility*) to intercourse and ejaculation (*sexual function*).

All of these organs and physiologic processes can be impaired by inflammation secondary to rheumatic diseases and could have detrimental effects on both reproductive function and pregnancy outcomes [5–7]. In addition, other well-known factors have detrimental effects on sexual health like chronic pain and fatigue, as well as psychological factors, such as depression and anxiety, all of them highly prevalent in patients with rheumatic diseases. Rheumatologists taking care of men with rheumatic diseases must consider this to adjust treatment accordingly. Improving men's preconception health might result in improved pregnancy outcomes by enhancing men's biologic and genetic contributions to the pregnancy conception (*pregnancy and offspring outcomes*) [8].

Information regarding the effect of rheumatic diseases on male sexual health is needed to improve the way rheumatologists counsel and treat male patients with rheumatic diseases.

Objective

The objective of our study was to systematically review the literature for the influence of paternal rheumatic disease on sexual health, such as sexual function, reproductive hormones, male fertility, pregnancy outcome and on their offspring health outcome. This systematic review (SR) will answer the following questions:

- What is the influence of rheumatic diseases on **male sexual function**?
- What is the influence of rheumatic diseases on **male fertility** and **reproductive hormones**?
- What is the influence of paternal rheumatic diseases on **pregnancy and offspring outcomes**?

Methods

Protocol and registration

This SR is part of a larger SR that included other immune-mediated diseases (IMD) from Gastroenterology and Dermatology. The complete protocol was registered in PROSPERO and is available in https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=99845. The protocol and this SR were written according to the PRISMA-P statement [9,10].

Search

A search strategy was developed by an experienced medical librarian (WMB) using a structured methodology [9,10]. The searches combined keywords regarding male sexual function and fertility, pregnancy outcomes and offspring's health with a list of IMDs (which included Rheumatic diseases). Our full electronic search strategy is provided in supplement 1.

Information sources

A systematic literature search was performed in the bibliographic databases: Embase (via Elsevier embase.com), MEDLINE via Ovid, Cochrane Central Register of Trials (CENTRAL) and Web of Science Core Collection. Additionally, Google Scholar and the Clinical trial registries of Europe and the USA were searched. We also contacted authors for further information and included references from the primary search publications, in case these were missed in our search. The databases were searched from inception until February 2019.

Eligibility criteria

The literature search was limited to the English language and human subjects. Case-control studies, cohort studies, cross-sectional studies, case reports and case series were included. Conference abstracts from before April 2016 were excluded if more recent conference abstracts were found we contacted the authors and searched for published data. Publications without original data, such as reviews, were excluded.

In the case of studies reporting pregnancy and offspring outcomes, publications were included if the diagnosis of the IMD took place before conception. In case of studies just reporting fertility parameters (i.e. semen analysis, sexual dysfunction) we included publications were the diagnosis of a rheumatic disease was taken into consideration. No restrictions were made in regard to the comparison groups. The outcome data should include at least one of the following outcomes; sexual function, reproductive hormones, fertility, pregnancy or offspring outcomes.

Study selection

All articles were imported into EndNote X9. After removal of duplicates with the method described by Bramer [11], two reviewers (LP and JC) independently and blindly screened titles, abstracts and full-text of the records for eligibility. Disagreements were resolved by consensus with the help of a third reviewer; RD, for sexual function, reproductive hormones and fertility outcomes and BW for pregnancy outcomes.

Data collection process

Two reviewers (LP and JC) extracted relevant information for each studied outcome from the included articles.

Risk of bias in individual studies

The methodological quality of the studies was assessed with the Newcastle Ottawa Scale (NOS), developed for case-control and cohort studies [12]. Case series were graded conform the cohort studies (without controls). In the case of cross-sectional studies, an adapted scale was used [13]. Using this method, points were awarded to each publication, related to the selection of the study group, the comparability of the study groups and the ascertainment of the outcomes. The score ranges from 0 to 9, with scores >5 representing good-quality studies. The results are presented in Tables 2–5. Quality assessment was done by LP and JC for the sexual function, reproductive hormones and fertility data, and the pregnancy and child outcome data by BW.

Synthesis of results

Sexual health outcomes were classified in 4 categories:

1. **Sexual function** (sexual dysfunction, premature ejaculation, erectile dysfunction).
2. **Reproductive hormones** (testosterone, LH, FHS, inhibin).
3. **Fertility** (sperm quality, testicular volume, time to pregnancy, number of children).
4. **Pregnancy and offspring outcomes** (congenital malformations, premature birth, impact on offspring).

Additional analysis

Due to the diversity of the methods used to report outcomes of interest in this SR performing a meta-analysis was not possible.

Results

Study selection

A total of 9735 references were identified (4505 from Embase, 3524 from Medline-Ovid, 1666 from Web of Science and 40 from Cochrane central) and imported into EndNote X9. After removing 2851 duplicates, 6884 articles were eligible for title and abstract screening. 6597 articles were excluded during this phase and 287 articles were eligible for full-text reading. 202 articles were excluded after full-text reading (see flowchart in Fig. 1) and 87 articles fulfilled the criteria for rheumatic diseases.

Summary of findings per disease

Results are presented per disease and divided into 4 categories (*sexual function, reproductive hormones, fertility outcomes and pregnancy and offspring outcomes*) (See Table 1).

Rheumatoid arthritis

Sexual function

Sexual function in RA was studied in 8 articles that included 282 patients with a mean age of 41.07 years. Three studies were in European populations, 3 in Africa, 1 in North America and 1 in Asia. Three articles assessed Sexual Dysfunction (SD) by interview, the International Index of Erectile Function (IIEF) was used in 3 articles, the Questionnaire for Screening Sexual Dysfunctions (QSD) in 1 article, and ICD-9 diagnosis code in 1 article.

The prevalence of SD was significantly higher in men with RA than in healthy controls in all the included studies (range, 33–62% vs 11–40%, respectively), this was associated with disease activity and other disease-related factors, such as fatigue and pain.

Elst et al. reported that 32 male patients with RA (mean age 46.2 ± 7 years) and a diminished functional capacity had lesser sexual motivation and that 9 (27%) of patients wanted advice from experts for their sexual problems [14]. SD was common in 32 RA patients (mean age 55 years), particularly impotence (defined as the inability to obtain an erection firm enough for vaginal penetration, or the inability to sustain the erection until completion of intercourse) was significantly more prevalent in RA patients than in age-matched controls (62% vs 40%, $p<0.05$).[15]

SD was reported in 49 out of 91 (53.8%) RA male patients (mean age 51.4 ± 9.4 years) in an Egyptian multicenter study. Using the IIEF, a statistically significant correlation between SD and several factors that are usually present in RA patients was reported. These factors were; pain, cardiovascular disease, age, disease activity, fatigue, tender joint count and psychological status. Interestingly, the number of intramuscular steroid injections, but not the oral intake of prednisone, was correlated with more SD [16].

Using the IIEF questionnaire in a case-control study, Gaber et al. assessed the prevalence of SD in 29 RA male patients (mean age 45.2 ± 12.1 years). A mean DAS28 score of 3.5 (standard deviation 1.45), suggestive of moderate disease activity was reported. Overall, SD was reported in 14 (48.3%) of patients vs 12 (33.3%) in controls (p = 0.2). All SD parameters were significantly higher in RA patients compared to controls and multivariate regression analysis revealed that severe RA (DAS28 >5.1) was associated with a higher risk of SD (OR 2.7, 95% CI 1.09-6.05) [17].

In a multicenter study from the Netherlands, van Berlo et al. included 76 male patients with RA (mean age 57.6 [standard deviation 10.6] years, mean DAS28 3.5 [standard deviation 1.45]) and found that RA patients differed significantly from 54 controls (mean age 54.9 [standard deviation 9.4]) regarding the frequency of sexual activities and libido (lower in RA than in controls, $p<0.05$). Physical functioning ($p<0.01$) and, to a lesser extent, disease duration and activity ($p<0.05$) significantly correlated with various sexual problems. Patients and controls did not differ regarding sexual satisfaction [18]. In a comparable study, Gordon et al. reported that among 31 RA patients (mean age 37 years), 10 (33%) admitted periods of erectile dysfunction (ED) and that 15 (50%) experienced decreased libido [19].

In a study comparing 24 male young RA patients (mean age 31.3 ± 7.35 years) and 18 age-matched healthy controls, Nasr et al. reported that SD was present in 11 (45.8%) of these patients compared to 2 (11.1%) controls. There were a significant correlation between dehydro-epiandrosterone sulfate (DHEA) levels, total and free testosterone levels and the IIEF score (p = <0.001) [20].

In a large population-based study from Taiwan that analyzed the data of 6319 patients diagnosed with ED, an association between ED and prior diagnosis of RA was reported. The OR for prior RA diagnosis among cases with ED was 1.67 (95%, CI 1.36–2.05) that of controls after adjusting for several confounders [21].

Reproductive hormones

Results on reproductive hormones were reported in 3 RA-related studies. In all of these studies, patients with RA were found to have lower total and free testosterone levels than healthy controls.

The androgenic status of 31 male patients with RA (median age 55 years) was investigated by Gordon et al., after correcting for age-related changes to the pituitary-testicular axis, patients with RA still showed significantly lower serum testosterone and significantly greater serum LH and FSH compared to 33 males with Ankylosing Spondylitis (AS) (median age 37 years) and 95 age-matched healthy controls. Serum FSH was significantly higher in RA patients compared to healthy controls [19].

Nasr et al. also studied the andrological profile of 24 men with RA (mean age 31.3 ± 7.3 years) and compared them to 18 healthy controls (mean age 30.8 ± 7.4 years). They found that RA patients have statistically significant lower DHEA (71.13 ± 22.71 vs 236.61 ± 105.41 ug/dl, $p<0.001$), total testosterone (1.5 ± 0.6 vs 4.7 ± 1.7 ng/ml, $p<0.001$) and free testosterone levels (32.7 + 14.2 vs 188.0 + 70.5 pg/ml, $p<0.001$) [20].

In one of the few prospective studies identified in this SR, a group of 41 RA male patients (mean age 53 years) were followed from disease onset through 2 years by Tengstrand et al. Early in the disease course, RA patients younger than 50 years had lower mean testosterone than controls (16.2 [standard deviation 3.5] vs 23.3 [standard deviation 7.5] UI/l, p=<0.001). A reduction of disease activity (lower DAS28 score) during the 2-year follow up correlated significantly with an increase in testosterone levels (r^s=−0.46, p = 0.006).[22]

Fertility

No studies were included.

Pregnancy and offspring outcomes

Using data from a nationwide Norwegian registry, Wallenius et al. reported no increased risk of adverse pregnancy outcomes or preeclampsia in partners of men with inflammatory joint disease, regardless of whether the father had or had not been exposed to Disease-Modifying Anti-Rheumatic Drugs (DMARDs) [23]. In a similar study, data from a Danish population-based cohort were presented by Rom et al. where paternal RA was not found to be associated with reduced fetal growth or preterm birth among 1086 children exposed to paternal RA compared to non-exposed children [24].

Systemic Lupus erythematosus

Sexual function

Sexual function in Systemic Lupus Erythematosus (SLE) was reported in 4 studies from Latin America, using the following outcome measures: IIEF in 1 article and interview in 3 articles. These studies included data on 229 patients with a mean age of 31.5 years and 175 healthy controls with a mean age of 28.8 years.

SD prevalence ranged from 12 to 68% in SLE patients compared to 0 to 22% in healthy controls. The association between disease activity and SD was analyzed in 2 studies and no association was reported [25,26]. In a multicenter study from Latin America that included 174 young SLE patients (mean age 36.1 ± 1.0 years) a significantly increased prevalence of ED in men with SLE compared to controls (68% vs 22%, p = 0.001) was reported. Among these patients the presence of persistent lymphopenia (≤1000 cells/mcl at three consecutive times, p = 0.006) and the use of prednisone (9.3 ± 1.2 vs 5.3 ± 1.2 mg, p = 0.026) were recognized as independent risk factors for ED (OR 2.79, CI95% [2.79–5.70], p = 0.001 and 2.15, CI95% [1.37–3.37], p = 0.001, respectively). Interestingly, only 7% of patients had been questioned about their sexual function in the previous 3 visits to the rheumatologist while 82% of the patients considered it would be appropriate to be asked about it [25].

Using a self-administrated questionnaire Silva et al. reported a prevalence of ED of 20% in 25 SLE young patients (mean age 26 years) compared to 0% in 25 healthy controls (mean age 27 years) (p=<0.0001) [26]. In 2 similar studies that also included young SLE patients (mean age 27 and 36 years, respectively), the prevalence of SD was found to be significantly higher in SLE patients compared to age-matched controls (12% vs 0% and 30 vs 0%, respectively) [27,28].

Reproductive hormones

Higher levels of FSH and LH, an indication of hypogonadism, in SLE patients compared to healthy control were a common finding in 5 studies included for this section. Unfortunately, the cause of hypogonadism in these men was not established.

In a study that included 25 young SLE patients (mean age 27 years [15–45]) and 25 age-matched healthy controls, it was shown that SLE patients had higher median FSH (5.8 [2.1–25] vs 3.3 [1–9.9] IU/L, p = 0.002) and higher median LH (5.8, CI95% [1.4–15.6] vs 3.7, CI95% [1.8–5.8] IU/L, p = 0.008) levels than controls. Low morning total testosterone levels were reported in 6 (24%) SLE patients compared to 0 controls [27]. Gonadal function was assessed by Soares et al. and they found that SLE patients with severe sperm abnormalities (azoospermia/oligospermia) had significantly higher median FSH level than patients with mild sperm abnormalities (10.9, CI95% [3.9–25] vs 3.3, CI95% [1–17.9] IU/L, p = 0.0001) [29].

Testicular cell function was determined by measuring serum inhibin B levels in a study that included 34 SLE patients (age 15–45 years) and it was reported that 8 (23.5%) patients had low serum inhibin B levels. This was associated with higher levels of FSH and LH and with lower sperm concentration, sperm count and motile sperm count [30]. In a small study that included 4 patients with juvenile-onset SLE, only one patient with sperm abnormalities had high FSH levels and a slight elevation of LH levels [31].

In a recent study by Tiseo et al. that included 28 young SLE patients (mean age 33 years) the median level of LH (6.5, CI95% [1.8–13] vs 3.95, CI95%[1.9–7.9] IU/L, p = 0.001) and total testosterone levels (500, CI95% [262–1500] vs 389, CI95% [162–729] ng/dl, p = 0.002) were significantly higher in SLE patients compared to 34 age-matched controls [32]. A potential limitation of this study was the exclusion of azoospermic SLE patients.

Fertility

Fertility parameters were reported in 9 studies, mainly from Brazil (n = 7). These studies included data on 263 SLE patients with a mean

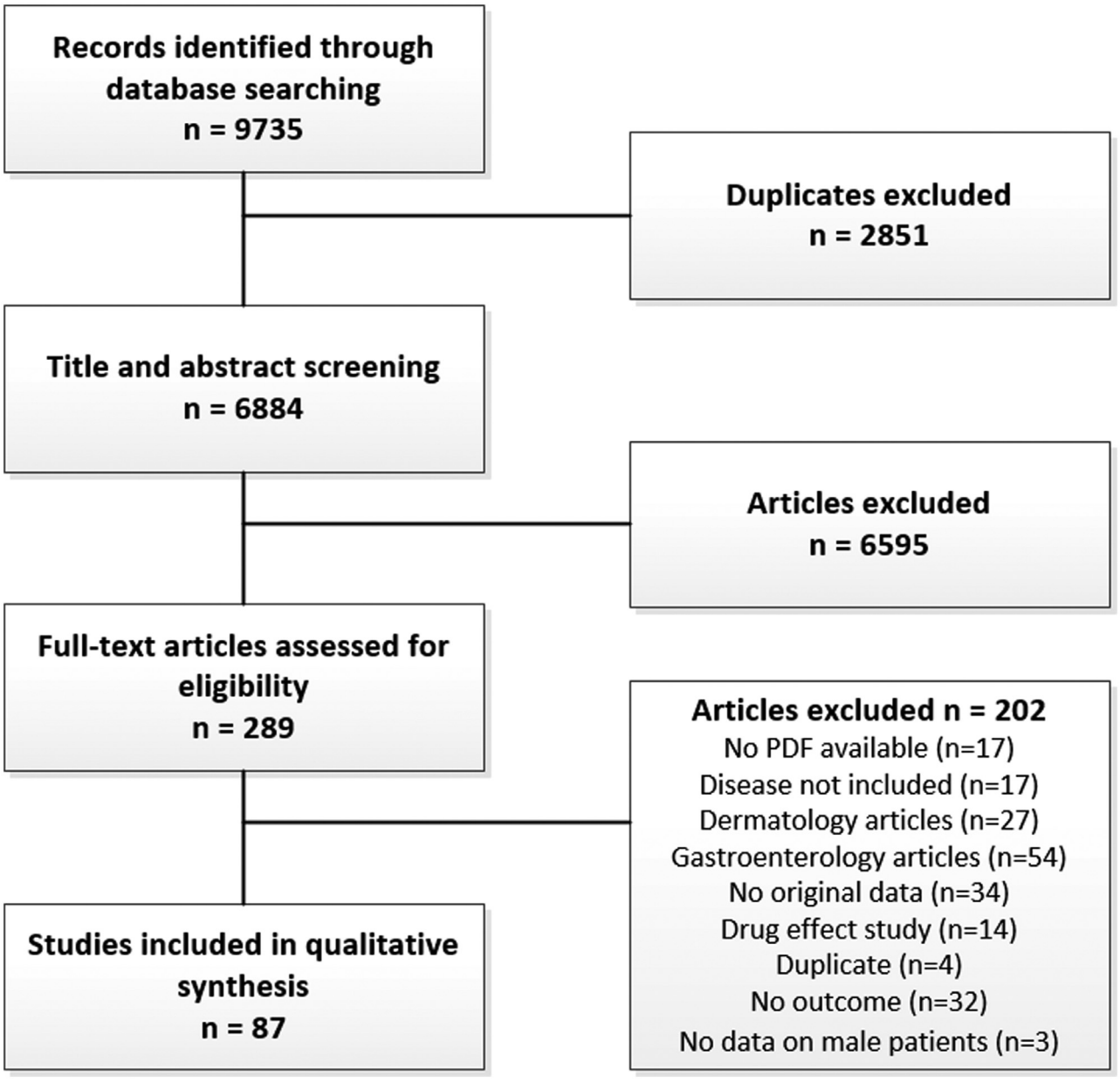

Fig. 1. Flowchart of study selection.

age of 30.2 years and 139 healthy controls with a mean age of 30.4 years. Sperm abnormalities, mainly lower median total sperm count, were a common finding in SLE patients. Infertility and subfertility as measured by the number of children per man, severe sperm abnormalities and the DNA fragmentation index (DFI) was also a relevant finding in 3 studies. Cyclophosphamide (CYC) was used in more than half of patients but could not solely explain these findings.

Soares et al. reported a significantly lower testicular volume in 35 SLE patients compared to controls (15 vs 20 ml, $p = 0.003$) and lower median total sperm count (70×10^6 vs 172×10^6, $p = 0.002$). In

Table 1
Number of articles included per disease.

Disease	Number of articles included	Sexual function	Reproductive hormones	Fertility	Pregnancy outcome
Rheumatoid arthritis	11	8	3	0	2
Systemic Lupus Erythematosus	10	4	5	8	0
Ankylosing Spondylitis	24	17	2	7	0
Systemic Sclerosis	7	7	0	1	0
Behçet Syndrome	9	5	0	4	1
Sarcoidosis	16	0	1	15	0
Antiphospholipid syndrome	4	2	0	3	0
Vasculitis	3	0	2	0	1
Auto-inflammatory syndromes	4	0	2	1	1

addition, all patients had semen abnormalities according to WHO guidelines [29]. In contrast, Suehiro et al. reported no difference in testicular volume among patients and controls [30].

Farhat et al. prospectively investigated the correlation of air pollutants exposure concentrations and semen quality in SLE patients and found that only CYC use and ozone had an association with sperm quality abnormalities. Even in patients not exposed to CYC a detrimental effect of ozone exposure on semen quality of SLE patients was observed [33].

Klinefelter syndrome (KS) may predispose men to develop SLE and primary testicular failure. An increased prevalence of KS in men with SLE was reported in a study that included 212 men with SLE (235 per 10,000 male SLE patients vs 17 per 10,000 in live male births). Interestingly, all SLE patients that were known to be infertile had KS. The authors went further recommending that any male SLE patient whose fertility is questionable should be evaluated for features of KS [34].

Regarding juvenile-onset SLE, a small study that included 4 patients (mean age 19 years) also demonstrated semen quality abnormalities in all of these patients; nonetheless, a medication effect could be responsible for these findings [31].

The integrity of genetic material in the spermatozoon is of essential importance for successful fertilization. The sperm DNA Fragmentation Index (DFI), a novel diagnostic tool used in infertility clinics, measures sperm DNA damage. DFI levels above 25% are strongly associated with infertility. DFI was significantly higher in SLE patients compared to controls (62, CI95% [31-97]% vs 25.5, CI95% [0-100]%, p=<0.001) in a study were conventional sperm parameters were similar in both groups. Interestingly, no correlations were found between DFI with disease activity (SLEDAI-2 K and SLICC/ACR-DI) or medication use [32].

Information about the number of children per man diagnosed with SLE was reported in 2 studies. In the study by Silva et al. the percentage of partners with gestations was statistically lower in SLE patients compared with 25 age-matched healthy controls (20% vs 60%, p = 0.0086).[26] Soares et al. reported that 20% of SLE patients fathered children after disease onset, compared with 80% controls (p = 0.0001) [29].

Pregnancy and offspring outcomes

No articles were included.

Antiphospholipid syndrome

Only 2 studies and 2 case reports of antiphospholipid syndrome (APS) patients were included.

In a small study that included 11 patients with APS (mean age 46.2 years), ED was observed more frequently in APS than in 22 age-matched controls (45.5% vs 4.5%) and previous arterial thrombosis was significantly higher in patients with ED compared to those without ED (100% vs 16.7%, p = 0.0152) [35].

ED was significantly higher in 12 APS patients (mean age 37.5 years) than in 20 age-matched controls (25% vs 0%, p = 0.044). Median sperm concentration, sperm motility, and normal sperm forms were comparable in APS patients and controls (141.5, CI95% [33–575] vs. 120.06, CI95% [34.5– 329]x10^6/ml, p = 0.65; 61.29, CI95% [25–80] vs. 65.42, CI95% [43–82]%, p = 0.4; 21.12, CI95% [10–42.5] vs. 23.95, CI95% [10– 45]%, p = 0.45, respectively), and none of them had oligo/azoospermia. The median penis circumference was significantly lower in APS patients with ED vs those without ED (8.1, CI95% [6–10] vs 10.2, CI95% [10–11] cm, p = 0.007) [36]. Testicular thrombosis secondary to APS was described in case reports [37,38].

Spondyloarthropathies

From the long list of diseases classified as spondyloarthropathies, our SR search strategy only identified articles that reported SD in AS (n = 15) and psoriatic arthritis (PsA) (n = 1).

Sexual function

A total of 15 studies were included in this section where many different questionnaires were used (IIEF used in 7 articles). In summary, 884 AS patients with a mean age of 37.9 years answered questionnaires or interviews for SD screening. Most of these studies are from Turkey [8], followed by Korea with 2 studies and India, Morocco, Tunes, China and Brazil with 1 study each. It was reported that SD can be a problem for 30–82.5% of male patients with AS (vs 12.5–43% in healthy controls), this was associated with disease activity, disease duration, depression, fatigue and limited joint mobility [39–54].

In a study that included 73 patients with AS, Rostom et al., reported that 70 (95.9%) patients had never been asked before by doctors about sexual activity [40]. Interestingly, 3 studies from Turkey reported a lower or similar prevalence of SD in patients and healthy controls [42–44]. Specific findings per article can be found in Table 2.

Reproductive hormones

Two studies performed an andrological evaluation in men with SpA. Hypogonadism was associated with inflammation in SpA patients in Italian patients [55] while in a Brazilian study the concentration of LH, FSH and testosterone was comparable among AS patients and healthy controls [56].

The Italian study included 10 young patients (mean age 28.7 ± 8.6 years) diagnosed with AS or PsA (n = 5/5) and a statistically significant difference in plasma hormone levels between patients and 20 age-matched healthy controls was detected: in patients LH and FSH values were higher (7.2, CI95% [4.5–7.9] and 5.7, CI95% [3.5–12.1] UI/L vs. 3.6, CI95% [3.1–4.2] and 3.4, CI95% [2.6–4.1] UI/L, respectively, both p=<0.01) and testosterone was lower (14.2, CI95% [9.9–18.1] vs. 20.4, CI95% [18.1– 22.5] nmol/L, p=<0.01). After 1 year of treatment with TNF inhibitors normal hormone levels were observed in this group [55].

Testicular Sertoli function was also evaluated in AS using inhibin B. It is considered an important marker of gonadal function and spermatogenesis. Median inhibin B levels were lower in AS patients and controls (68, CI95% [23–265] vs 112.9, CI95% [47.8–231.9] pg/ml, p = 0.111). Other hormones, such as FSH and LH were similar in both groups [56].

Fertility

Five studies analyzed the impact of AS on sperm quality and reported inconsistent results. In total, data from 158 SpA patients, mainly diagnosed with AS (mean age 32.9 years) and 231 healthy controls (mean age 33.5 years) were included. This population was more heterogeneous, 3 studies are from Europe, 1 from Latin America and 1 from Asia. No differences in the semen quality between patients and healthy controls were reported in 3 studies, but the presence of varicocele was significantly higher in patients compared to controls in 2 studies and this was associated with semen quality abnormalities. In 2 studies, sperm motility was significantly reduced in SpA patients. This was associated with disease activity and improved after treatment with TNF inhibitors. In addition, an increased rate of infertility was reported in one study.

Ramonda et al. detected a significant reduction in the percentage of progressive and non-progressive motile sperm in 10 AS patients (mean age 28.7 years) compared to 20 age-matched controls. Importantly, a possible influence of disease activity on semen quality was detected as these abnormalities improved after treatment with TNF

Table 2
Summary of sexual function results.

Study	Number of cases/controls (mean age in years)	Diagnostic/Screening tool used	Main findings	Study type and Quality assessment (NOS)
Rheumatoid arthritis				
Elst [14] Netherlands	Cases: 32 (46.2 ± 7) Controls: 236 (NA)	Interview and sexual motivation scale	Impotence was significantly more prevalent in RA patients than in age-matched controls (62% vs 40%, $p<0.05$) Patients with tender joint count <6 had stronger sexual motivation than those with >6. No statistically significant difference was found between disease activity and lower sexual interaction. 27% of patients wanted advice for their sexual problems	Case-control 2
Blake [15] USA	Cases: 32 (57.2) Controls: 21 (55.1)	Interview and the Azrin Marital Happiness Scale (AMHS).	Impotence prevalence was statistically significant in RA patients compared to controls (62% − 40%). • Associated with older age, DM2, hypertension and methotrexate use. Depression was not associated with impotence.	Case-control 5
El Miedany [16] Egypt	Cases: 91 (51.4 + 9.4) Controls: NA	IIEF	SD reported by 53.8% of male patients with RA. SD correlated with: • Pain score, cardiovascular disease, age, disease activity, psychological status, fatigue score, number of intramuscular steroid injection, tender joint count. No correlation with DMARDs or oral steroid therapy.	Cohort 2
Gaber [17] Egypt	Cases: 29 (45.2 ± 12.1) Controls: 36 (43.2 ± 9.7)	IIEF	SD present in 48.3% of RA patients (33.3% in controls). SD significantly associated with: • Longer morning stiffness duration. • Higher DAS28 score.	Case-control 3
Van Berlo [18] Netherlands	Cases: 76 (57.6 [SD 10.6]) Controls: 54 (54.9 [SD 9.4])	Questionnaire for screening sexual dysfunctions (QSD)	Statistically significant differences among RA patients and controls: • Feel any desire for sexual contact with their partner (85% vs 96%) • Masturbate (52% vs 79%). • Have sexual daydreams or fantasies (65% vs 89%). Physical functioning, disease duration and activity correlated with various sexual problems. 41% of men had troubles with several joints during sexual activities.	Case-control 6
Gordon [19] Scotland	Cases: 31 (55) Controls: 95 (NA)	Interview	33% of RA patients admitted periods of impotence and 50% experienced decreased libido.	Case-control 3
Nasr [20] Egypt	Cases: 24 (31.3 ± 7.3) Controls: 18 (30.8 ± 7.4)	IIEF	45.8% of patients with RA were diagnosed with ED compared to 11.1% of controls. • 20.8% of RA patients had moderate ED compared to 0% of controls. No significant correlation found between IIEF and disease activity. Significant correlation found between dehydroepiandrosterone (DHEA) levels, total and free testosterone levels and IIEF score.	Case-control 4
Keller [21] Taiwan	Cases:6310 (NA) Controls: 37,860 (NA)	ICD-9 diagnosis	The OR for prior RA among cases with ED was 1.67 (95%, CI 1.36 − 2.05) that of controls after adjusting for several factors.	Cohort 4
Systemic lupus erythematosus				
Merayo-Chalico [25] Mexico	Cases: 174 (36.1 ± 1.0) Controls: 105 (NA)	IIEF	Prevalence of SD in SLE patients was 68% vs 22% in healthy controls ($p = 0.001$). Significant differences were reported among patients with SLE and SD and those without SD: • Presence of persistent lymphopenia (≤1000cells/mcl at three consecutive times, $p = 0.006$). • Higher prednisone dose (9.3 ± 1.2 vs 5.3 ± 1.2 mg, $p = 0.026$). • SLICC damage score (1.25 ± 0.14 vs 0.80 ± 0.16 points, $p = 0.042$). No difference regarding disease activity (SLEDAI score 4.89 ± 0.54 vs 3.65 ± 0.52, $p = 0.16$). Only 7% of patients had been questioned about their sexual function. • 82% of patients considered it would be appropriate to be asked about their sexual function	Cross-sectional 4
Silva [26] Brazil	Cases: 25 (26) Controls: 25 (27)	Interview	SD present in 20% of SLE patients compared to 0% in healthy controls ($p = 0.0001$). The SLEDAI [0 (0–12) vs 0 (0–6), $P = 0.295$] and SLICC/ACR-DI [0 (0–1) vs 0 (0–3), $P = 0.36$] medians were similar in SLE patients with SD/ED in comparison with those with normal function.	Case-control 3
Rabelo-Junior [28] Brazil	Cases: 10 (36.9) Controls: 20 (32.4)	Self-administered non specified questionnaire	SD significantly higher in SLE patients compared to controls (30% vs 0%, $p = 0.029$).	Cross-sectional 5
Vecchi [27] Brazil	Cases: 25 (27) Controls: 25 (27)	Interview	SD present in 12% of SLE patients vs 0% in controls, $p = 0.0638$. None of the patients or controls had ED. Frequency of sexual intercourse was similar among both groups.	Case-control 8

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Table 2 (*Continued*)

Study	Number of cases/controls (mean age in years)	Diagnostic/Screening tool used	Main findings	Study type and Quality assessment (NOS)
Antiphospholipid syndrome				
Lopes Gallinaro [35] Brazil	Cases: 11 (46.2 ± 9.4) Controls: 22 (42.3 ± 6.0)	IIEF	SD was significantly observed more frequently in APS than controls (45.5% vs 4.5%, p = 0.0096). Moderate/severe ED was more common in APS than controls (36.4% vs 0%, p = 0.0081). Erectile function and intercourse satisfaction were the areas with the most significant differences among APS patients and controls. Arterial events were significantly higher in APS patients with SD than those without SD (100% vs 16.7%, p = 0.0152).	Cross-sectional 4
Rabelo-Junior [36] Brazil	Cases: 12 (37.5) Controls: 20 (32.4)		Erectile dysfunction was significantly higher in APS patients than in controls (25% vs 0%, p=−0.044). 42% of APS patients with previous arterial thrombosis had SD compared with no patients with arterial events (p = 0.204).	Cross-sectional 5
Spondyloarthropathies				
Dhakad [39] India	Cases: 100 (34.42 ± 9.78) Controls: 100 (36.39 ± 8.07)	IIEF	SD was more common in AS patients: • Erectile function, orgasmic function, intercourse satisfaction and overall satisfaction were found to be significantly lower in the AS group as compared to controls . ED in 42% of AS patients (vs 18% in controls, p = 0.0006) • Associated with higher age, longer AS duration, anxiety, depression and higher BASFI.	Case-control 5
Rostom [40] Morroco	Cases: 110 (38.9 ± 12.5) Controls: NA	Self-administered questionnaire	95.9% had never been asked about sexual activity by their doctors and 41% discussed the impact of AS on sexual activity with their partners. From those sexually active: • 44% were unsatisfied. • 41% reported ED. • 38.4% had orgasmic problems. What is the cause of your sexual problems? • Fatigue (90%). • Pain (69%). • Depression (62.5%).	Cross-sectional 2
Sariyildiz [41] Turkey	Cases: 70 (36.4 ± 7.4) Controls: 60 (35.2 ± 7.7)	IIEF	Patients with AS had significantly lower scores in each of the 5 domains of the IIEF compared to healthy controls (p=<0.05). Negative correlation between BASFI scores and IIEF scores (p=<0.01). • BASFI was independently associated with orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. BASDAI negatively correlated with erectile function, intercourse satisfaction and IEEF total scores (p=<0.05). • BASMI was independently associated with erectile function ($p < 0.05$)	Cross-sectional 4
Rezvani [42] Turkey	Cases: 39 (38) Controls: 27 (30)	IIEF	Prevalence of ED was higher in healthy controls compared to patients with AS (51.9% vs 43.%, respectively, p = 0.512).	Case-control 3
Tarhan, [43] Turkey	Cases: 50 (38.5 ± 10.3) Controls: 50 (38.7 ± 7.0)	Interview	Similar prevalence of premature ejaculation in AS patients and healthy controls (32 and 30%, p = 0.331).	Case-control 3
Ozkorumak [45] Turkey	Cases: 43 (36.2 ± 8.7) Controls: 43 (36.5 ± 6.5)	DSM-IV criteria (diagnosis confirmed by psychiatrists) and Glombok-Rust Inventory of Sexual Satisfaction (GRISS)	SD diagnosis established in 41.9% of patients vs 14.6% of controls (p = 0.08). GRISS total score modestly correlated with depression and anxiety scores and with disease activity (BASDAI). GRISS scores significantly higher in AS patients than controls. Significant differences in: • Premature ejaculation • Dissatisfaction • Impotence	Cross-sectional 5
Bal [44] Turkey	Cases: 37 (42.8 ± 10.8) Controls: 67 (43.6 ± 5.9)	IIEF	Prevalence of ED similar between patients and controls (35.1% vs 26.9%, p = 0.335). The only statistically significant difference was detected in sexual desire (lower in AS patients, p = 0.014). No correlation between IIEF scores, AS disease duration and activity parameters was reported.	Cross-sectional 4
Oh [46] Korea	Cases: 22 (37.8) Controls: NA	IIEF	63.6% of AS patients had ED. • Decreased to 45.5% after 3 months of anti-TNF therapy. There were significant improvements in 4 IIEF-5 domains after 3 months of anti TNF therapy (all except orgasmic function).	Cross-sectional 2

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Table 2 (*Continued*)

Study	Number of cases/controls (mean age in years)	Diagnostic/Screening tool used	Main findings	Study type and Quality assessment (NOS)
Cakar [47] Turkey	Cases: 53 (32.8 ± 12.1) Controls: NA	Interview "According to you, does AS affect you negatively during sexual intercourse?"	50.94% of AS patients admitted as affected with regard to sexual intercourse. Patients with lumbar column and hip involvement and those with higher depression scores were more likely to report sexual intercourse dissatisfaction.	Cross-sectional 3
Dincer [48] Turkey	Cases: 65 (32.98 ± 11) Controls: 45 (30.1 ± 6.2)	Brief Male Sexual Function Inventory (BMSFI)	Patients with AS had significantly lower sexual drive, problem assessment, erection and overall satisfaction scores compared with healthy controls. 20.5% of AS patients were significantly more likely to report that they were not sexual satisfied vs 8.8% of healthy controls (p=<0.05). SD associated with depression and limited joint mobility (BASMI)	Case-control 6
Pirildar [49] Turkey	Cases: 65 (36 ± 8.1) Controls: 65 (37 ± 5.2)	IIEF	AS patients had significantly lower erectile function, orgasmic function, intercourse and overall satisfaction scores (p=<0.05). 12% with AS had mild or moderate ED (controls not reported). ED was associated with morning stiffness (>4 h).	Case-control 4
Shen [51] China	Cases: 78 (40) Controls: NA	Modified Body Image Questionnaire	56.3% of AS patients reported impaired sexual function (vs 29.8% in controls, p<0.001). Disease activity, body image disturbance and physical impairments were linked with impaired sexual functioning.	Cross-sectional 5
Younes [52] Tunisia	Cases: 42 (36 ± 8.1) Controls: NA	Interview	44% AS patients reported sexual problems and 40% reported negative reactions of their spouses to the disease. BASMI >4 was associated with sexual problems.	Cross-sectional 5
Santana [53] Brazil	Cases: 40 (45.8 ± 11.4) Controls: 40 (46 ± 11.1)	IIEF	IIEF total score was lower in AS patients than in controls (22 vs 29 points, P=<0.0001). 82.5% of AS patients had mild to severe ED compared to 12.5% of controls (p=<0.001). Disease activity (BASDAI) was associated with sexual impairment (p=<0.001)	Cross-sectional 3
Gallinaro [54] Brazil	Cases: 28 (43.9) Controls: 28 (38.4)	Interview Sexual activity questionnaire	61.9% of patients reported pain after sexual relationship, spine mobility was reduced in 95.2% of these patients. 85.% of patients reported achieving sexual satisfaction. Correlation with longer disease duration and higher disease activity scores (BASFI, BASDAI)	Cross-sectional 4
Systemic sclerosis				
Hong [68] Canada & USA	Cases: 48(52 ± 1.7) Controls: 55 (53 ± 2.3)* *Controls: RA patients	IIEF	ED prevalence was significantly higher in SSc patients than RA patients (81% vs 48%, p=<0.05). For the majority of these patients, ED symptoms began after disease onset. Raynaud's phenomenon (RP) was associated with ED (Relative risk (RR)=4.0, p=<0.01).	Case-control 3
Ostojic [62] Serbia	Cases: 5 (38.8) Controls: NA	IIEF	3/5 patients reported that impotence occurred "very early" in their disease (average 4 months after first symptom). Patients with ED had: • Higher skin scores. • More lung fibrosis on chest X-rays. • More restrictive lung disease. 1 patient developed Peyronie's disease (fibrosis of corporal body and penile skin).	Case series 8
Proietti [63] Italy	Cases: 14 (41) Controls: NA	IIEF Duplex ultrasound (US)	Almost all patients were found to have moderate or severe degrees of vasculogenic SD. Erectile function domain score were significantly improved by once-daily tadalafil (13.0 ± 6.8 to 17.0 ± 9.0, p < 0.05)	Cohort 2
Rosato [64] Italy	Cases: 20 (49) Controls: NA	IIEF Videocapillaroscopy Doppler US	All patients presented moderate to severe ED (100%). Reduction of arterial flow was present in all SSc patients. Venocclusive dysfunction was evident in 55% patients. A high degree of arteriolar damage was evident. No association with videocapillaroscopy abnormalities.	Cross-sectional 6
Foocharoen [66] European multicenter	Cases: 130 (52.3) Controls: NA	IIEF	81% of SSc patients had variable degrees of ED. • The largest group of all participants (38%) had severe ED. • 90.1% of patients reported that ED began after disease onset. The presence of ED was associated with more severe organ involvement.	Cohort 5
Sanchez [67] France	Cases: 13 (55.9) Controls: NA	IIEF	ED was found in 87.5% of SSc patients (mean IIEF-5 score 21 (mean [SD]: 16.0 [5.3]).	Cross-sectional 6
Aversa [65] Italy	Cases: 15 (47 ± 12.5) Controls: NA	IIEF Doppler US	High incidence of ED (86%, mean IIEF score 13.3), positively correlated with age and disease duration. All of the patients (irrespective of ED status) had a marked reduction of arterial flow with the presence of concomitant mild venoocclusive dysfunction in 66%.	Case-series 8

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Table 2 (*Continued*)

Study	Number of cases/controls (mean age in years)	Diagnostic/Screening tool used	Main findings	Study type and Quality assessment (NOS)
			Morphology of cavernous arteries at power energy revealed the presence of high degree of arteriolar damage.	
Behçet Syndrome				
Erdogru [69] Turkey	Cases: 24 (39.1) Controls: NA	Interview	*Patients with Neuro- Behçet. ED was present in 63% of BS patients. 58% of ED were classified as mixed vasculogenic.	Cross-sectional 3
Aksu [70] Turkey	Cases: 2 (45) Controls: NA	Interview	Case report 2 patients with BS and ED caused by severe venous leak detected by penile Doppler US and cavernosography.	Case report
Hiz [71] Turkey	Cases: 42 (33.7 ± 7.2) Controls: 42 (34.5 ± 4.9)	IIEF Beck Depression Inventory (BDI)	IIEF scores were significantly lower in BS patients than controls (20 vs 29, $p = 0.001$). The mean BDI score was found to be significantly higher in the patient group compared to the control group ($P < 0.001$). The IIEF score was not related to active skin findings, active oral ulcers, active genital ulcers, eye involvement, or medication for BS, but it was related with history of arthritis.	Case control 4
Gul [72] Turkey	Cases: 24 (35.8 ± 8.9) Controls: 24 (37.3 ± 9.8)	GRISS and Arizona Sexual Experience Scale (ASEX)	SD was present in 80% of participants compared to 32% of healthy controls ($p = 0.0001$). SD was significantly more frequent in patients with depression than those without it (93 vs 61%, $p = 0.001$). Significantly higher levels of impotence, premature ejaculation and satisfaction subscale scores in BS patients than in controls.	Case-control 3
Batmaz [73] Turkey	Cases: 72 (35.5 ± 7.8) Controls: 62 (36.5 ± 4.9)	IIEF	Patients with BS scored significantly lower in IIEF scores than healthy controls. Associated with: Age, duration of disease, depression and quality of life. No association was found between IIEF scores and medication use, active oral/genital ulcers, ocular involvement, venous thrombosis and arthritis.	Cross-sectional 2

inhibitors [55]. Micu et al. included baseline semen samples for 20 patients (mean age 34.7 years [S.D. 9.2]) with high disease activity (mean BASDAI 7.5 [S.D. 1.1] and mean CRP 2.9 mg/dl [95% CI 2.1, 3.6]). Interestingly, no statistically differences were noticed when comparing samples from active patients and healthy controls (normospermia in 91% vs 71.4%, respectively [57]. No differences in sperm quality between AS patients and healthy controls were reported in other studies [56,58] (See Table 4).

In a small study from Villiger et al. semen quality of 26 SpA patients with and without TNF inhibitors was compared. Sperm abnormalities were more frequent in patients without TNF-inhibitors (10/11) than in patients with TNF-inhibitors (11/15). Patients without TNF-inhibitors had poorer sperm motility and vitality ($p = 0.001$). No significant correlation between disease activity (BASDAI/C-Reactive protein) and sperm quality was reported [59].

The incidence of varicocele was significantly higher in AS patients than in healthy controls in two studies (40 vs 8%, $p = 0.027$ and 52 vs 20%, $p = 0.009$). This was also associated with sperm abnormalities [58,60].

In a study by Uzunaslan et al., an increased rate of infertility in men after a diagnosis of AS was reported (9.1% vs 2.9% in healthy controls, $p = 0.404$) and AS patients had fewer children than healthy controls (1.921 vs 2.466, $p = 0.013$).[61]

Pregnancy and offspring outcomes

No articles were included.

Systemic sclerosis

Sexual function

Seven studies that included 24 Systemic Sclerosis (SSc) patients with a mean age of 47.2 years fulfilled the inclusion criteria (6 studies from Europe and 1 from North America). Using the IIEF in 7 studies, the prevalence of SD in men with SSc was very high, ranging from 60% to 100% (healthy controls were not included in these studies). Damage to small blood vessels and fibrosis are responsible for many of the clinical manifestations of SSc. These factors are also important in the pathogenesis of SD and the association between them and the presence of SD in men with SSc has been studied by several groups.

In a small case series that included 5 young patients with SSc (mean age 38.8 years) Ostojic et al. reported the impact of microvasculopathy and fibrosis on the development of ED in men with SSc. They found that ED was present in 60% of their patients. ED was a frequent early clinical feature of SSc (average 4 months after presenting the first symptom). Although microvascular abnormalities were not associated with ED, fibrotic changes in the lungs were more frequently reported in patients with ED. Interestingly, Peyronie's disease, a fibrotic condition of the penis, developed in one SSc patient [62].

The extent of penile damage was investigated by Proietti et al. in 14 patients with diffuse or limited SSc by evaluating cavernous artery flow. They found that almost all patients had moderate or severe degrees of vasculogenic-SD. Both, erectile function and vascular measures of cavernous arteries improved after once-daily tadalafil intake [63].

To investigate the association between vascular damage and ED in SSc patients, Rosato et al. enrolled 20 SSc patients (mean age 49 years) and found that all had moderate to severe ED. Together with ultrasound (US) findings, it was concluded that all of them had vasculogenic ED [64].

Aversa et al. included 15 patients with SSc in a study that used US to describe the penile vasculature in SSc. A high prevalence of ED (86%, mean IIEF score 13.3) was reported. All patients (irrespective of ED status) had a marked reduction of arterial flow with the presence of concomitant mild venoocclusive dysfunction in 66% of them [65].

In the largest study known to date, a multicenter European cohort, data of 130 SSc patients was collected and a prevalence of ED of 81% (105/130) was reported. 40 (38%) patients had severe ED (IIEF-5 score

Table 3
Summary of reproductive hormones.

Study	Number of cases/controls (mean age in years)	Main findings	Study type and Quality assessment (NOS)
Rheumatoid arthritis			
Gordon [19] Scotland	Cases: 31 (55) Controls: 95 (NA)	Patients with RA compared to AS patients and healthy controls showed significantly: • Lower serum testosterone (p=<0.05). • Significantly greater serum LH (p=<0.05). Serum FSH was significantly higher in RA patients compared to controls but not in AS patients. Serum testosterone levels showed significant negative correlations with ESR and RF titers.	Case-control 3
Nasr [20] Egypt	Cases: 24 (31.3 ± 7.3) Controls: 18 (30.8 ± 7.4)	Patients and controls showed statistically significant differences in: • Lower DHEA (mean ± SD: 71.13 ± 22.71 vs 236.61 ± 105.41 ug/dl, p = 0.000). • Lower total and free testosterone (mean ± SD: 1.5 ± 0.69 vs 4.72 ± 1.75 ng.ml, p = 0.000).	Case-control 4
Tengstrand [22] Sweden	Cases: 40 (53) Controls: 131 (NA)	Compared to controls, patients younger than 50 years had: • Lower testosterone concentrations (16.2 [3.5] vs 23.3 [7.5], [=<0.001). • Lower SHBG concentrations (26 [7] vs 34 [12], p = 0.20). • Lower NST concentrations (11.2 [2.5] vs 14.9 [4.5], p = 0.004) Patients older than 50 years had on average significantly lower LH levels than controls (4.3 [3.3] vs 6.2 [2.1]. p = 0.001). **After 2 year follow-up:** Mean testosterone levels increased in the responder group but were unchanged in the non-responders (17.7 [5.8] vs 13.9 [3.5], p = 0.25). Lower disease activity did not affect LH, which remained low during the 2 years follow-up period.	Case-control 6
Systemic lupus erythematosus			
Vecchi [27] Brazil	Cases: 25 (27) Controls: 25 (27)	Median of FSH and LH were significantly higher in SLE patients versus controls (5.8 vs. 3.3 IU/l; 5.8 vs. 3.7 IU/l; respectively, p = 0.002). The frequencies of elevated FSH and lower morning total testosterone levels were significantly higher in SLE patients compared with controls (28% vs. 0%; 24% vs. 0%; respectively, p = 0.009).	Case-control 8
Soares [29] Brazil	Cases: 35 (28.9 ± 8.8) Controls: 35 (29.1 ± 8.9)	FSH levels were higher in SLE patients with severe sperm abnormalities (3.3 [1–17.9] vs 10.9 [3.9–25] IU/l). Elevated FSH levels were detected in 42.9% of patients who underwent IV CYC therapy compared with 9.5% of those who did not.	Case-control 6
Suehiro [30] Brazil	Cases: 34 (30) Controls: NA	Eight SLE patients (23.5%) had low serum inhibin B levels (Group 1, median 11.05 pg/ml) and 26 (76.5%) had normal serum levels (Group 2, median 141.05 pg/ml). Elevated FSH levels were detected in 100% of the patients of Group 1 compared with none in the normal serum inhibin B Group.	Cross-sectional 3
Silva [31] Brazil	Cases: 4 (19) Controls: NA	Normal hormone levels in patients (FSH, LH, prolactin, testosterone).	Case-series 7.5
Tiseo [32] Brazil	Cases: 28 (33) Controls: 34 (36.5)	Median of LH (6.5 vs 3.95 IU/L) and total testosterone levels (500 vs 389 ng/dl) were significantly higher in SLE patients compared to controls (p = 0.001).	Case-control 6
Spondyloarthropathies			
Ramonda [55] Italy	Cases: 10 (28.7 ± 8.6) Controls: 20 (27.4 ± 4.2)	In AS patients LH and FSH values were higher (7.2 and 5.7 UI/L vs. 3.6 and 3.4 UI/L) and testosterone was lower (14.2 vs. 20.4 nmol/L) (p = 0.01).	Case-control 4
Almeida [56] Brazil	Cases: 20 (33) Controls: 24 (28.5)	The median inhibin B levels were comparable in AS patients and controls (68 vs 112.9 pg/mL, p = 0.111). The median of FSH levels (3.45 vs. 3.65 IU/L) and the other hormones were also similar in both groups.	Cross-sectional 4

<7) [66]. Similarly, Sanchez et al. and Hong et al. reported an ED prevalence of 87.5% and 81%, respectively [67,68].

Fertility

The number of children per man can be considered as a good proxy of fertility. Hong et al. compared this parameter in 48 patients with SSc and 55 patients with RA and they found that patients with SSc had significantly fewer biological children than those with RA [2.0 ± 0.2 (0.4) vs 2.7 ± 0.2 (0.5), respectively, p=<0.01]. Among patients with SSc, and to a lesser extent RA, the presence of Raynaud's phenomenon (RP) was significantly associated with this finding (80% of patients with RP had ED vs 50% of patients without RP, p=<0.01) [68].

Reproductive hormones and pregnancy and offspring outcomes

No articles were included.

Behçet syndrome

Sexual function

Sexual function in Behçet's syndrome (BS) was reported in 5 studies from Turkey, using the following outcome measures: IIEF in 2 articles, interview in 2 articles and the Arizona Sexual Experience Scale (ASEX) in 1 study. These studies included data on 164 patients with a mean age of 37.2 years and 128 healthy controls with a mean age of 36.1 years. In this group, the prevalence of SD ranged from 63 to 80% in BS and 32% in healthy controls.

In a small study of 19 male patients (mean age 39.1 years) diagnosed with Neuro-Behçet, ED was reported in 12 (63%) patients. Mixed vasculogenic impotence was responsible for 63% of ED cases [69]. Inspired by these findings, Aksu et al. reported 2 cases of ED in patients with BS, they determined that the cause of ED was severe venous leak possibly secondary to disease-related thrombosis [70].

In the first study that used standardized methods (IIEF) to screen for SD in 42 BS patients (mean age 33.7 years), Hiz et al. found that the total IIEF score was significantly lower in BS patients compared to 42

Table 4
Summary of fertility outcomes.

Study	Number of cases/controls (mean age in years)	Main findings	Study type and Quality assessment (NOS)
Systemic lupus erythematosus			
Silva [26] Brazil	Cases: 25 (26) Controls: 25 (27)	Percentage of partner with gestation was statistically lower in SLE patients compared to controls: • 20% vs 60% (p = 0.0086) Regarding gonadal function: • 60% of SLE patients vs 0% if controls presented sperm quality abnormalities (p = 0.001). • Reduction of testicular volume correlated to semen abnormalities severity (suggestion of severe lesion of the seminiferous tubules).	Case-control 3
Rabelo-Junior [28] Brazil	Cases: 10 (36.9) Controls: 20 (32.4)	Median right testicular volume by US was significantly lower in SLE-APS patients (10.38 (3.9–16.7) vs. 13.4 (8.5–20.6) mL, p = 0.03). Median values of sperm concentration and sperm motility were significantly lower in SLE patients: • Sperm concentration (41.1 [0–145] vs 120 [34.5–329] x 10^6/ml, p = 0.003). • Sperm motility (47.2 [0–87.5] vs 65.42% [43–82], p = 0.047). Median penis circumference was significantly reduced in SLE-APS patients with ED compared to patients without ED (8.17 [8–8.5] vs. 9.14 [7–10.5] cm, p = 0.0397).	Cross-sectional 5
Farhat [33] Brazil	Cases: 26 (29.8) Controls: NA	An increase of 23.5 ug/m3 of ozone averaged over the 0–90 day period before collection of sample was associated with a decrease of 30.6 million spermatozoa/ml (95% CI, 2.0–59.3; p = 0.040). No effects were observed with other pollutants.	Cross-sectional 3
Vecchi [27] Brazil	Cases: 25 (27) Controls: 25 (27)	The median testicular volume by right and left Prader was significantly lower in SLE compared with controls (15 vs. 20 ml and 15 vs. 20 ml; respectively), p = 0.006. Median penis length and circumference were significantly lower in SLE compared with controls (8 vs. 10 cm, p = 0.0001). The frequencies of oligo/azoopermia (44 vs. 0%, p = 0.0002) and asthenozoospermia (36 vs 0%, p = 0.0016) in SLE patients were higher than controls. The median of sperm concentration, total sperm count, total motile sperm count, sperm motility and normal sperm by WHO guidelines were uniformly and significantly lower in SLE patients versus controls.	Case-control 8
Soares [29] Brazil	Cases: 35 (28.9 ± 8.8) Controls: 35 (29.1 ± 8.9)	The median of the testicular volume in both testes according to Prader orchidometry were significantly lower in SLE patients than in controls (15 ml vs 20 ml at the right testicle [p = 0.003] and 15 ml vs 20 ml at the left testicle [p = 0.004]). All 35 male SLE patients (100%) had semen abnormalities according to WHO guidelines: • SLE patients had a lower median total sperm count (70 × 10^6 vs 172 × 10^6, p = 0.002) and a lower median total motile sperm count (32 × 10^6 vs 119 × 10^6, p = 0.004) compared with controls. Seven SLE patients (20%) fathered children after disease onset, compared with 28 controls (80%), p = 0.0001. No significant difference regarding the presence of varicocele among both groups.	Case-control 6
Suehiro [30] Brazil	Cases: 34 (30) Controls: NA	No significant difference in testicular volume in SLE patients with low or normal inhibin B levels. Patients with low inhibin B levels had lower median sperm concentration (2 vs 56.5 10^6/ml, p = 0.024), total sperm count (6 vs 133 10^6/ml, p = 0.023) and total motile sperm count (3 vs 69.5 10^6/ml, p = 0.025) compared with patients with normal inhibin B levels. Inhibin B levels were positively correlated with sperm concentration and total motile sperm count. No significant difference regarding the presence of varicocele among both groups.	Cross-sectional 3
Scofield [34] USA	Cases: 76 (NA) Controls: NA	Klinefelter's syndrome (KS) prevalence of 264 per 10,000 men with SLE (>15 times higher than the general population) "Are you infertile?" • All men subsequently found to have KS answered the question with a response other than "no". • This question was 100% sensitive and 33% specific for identification of KS in men with SLE.	Cohort 4
Silva [31] Brazil	Cases: 4 (19) Controls: NA	Normal testicular volume in 100%. Sperm quality abnormalities in 100%.	Case-series 7.5
Tiseo [32] Brazil	Cases: 28 (33) Controls: 34 (36.5)	The sperm DNA fragmentation index (DFI) was significantly higher in SLE patients compared to controls (62 [31–97] vs 25.5 [0–100]%, p=<0.001) in a study were conventional sperm parameters were similar in both groups. No correlations were evidenced between DFI with multiple variables: age, BMI, disease duration, disease activity, cumulative doses of prednisone, cyclophosphamide, methotrexate, azathioprine or mycophenolate mofetil.	Case-control 6
Antiphospholipid syndrome			
Rabelo-Junior [36] Brazil	Cases: 12 (37.5) Controls: 20 (32.4)	Sperm quality was comparable in APS patients and controls: • Sperm concentration: 141.5 [33–575] vs. 120.06 [34.5– 329] 10^6/ml, p = 0.65. • Sperm motility: 61.29 [25–80] vs. 65.42 [43–82]%, p = 0.4. • Normal sperm morphology: 21.12 [10–42.5] vs. 23.95 [10– 45]%, p = 0.45.	Cross-sectional 5
Rabelo-Junior [28] Brazil	Cases: 10 (36.9) Controls: 20 (32.4)	Median values of sperm concentration (41.1 vs. 120.06 × 10^6/mL, p = 0.003) and sperm motility (47.25 vs. 65.42%, p = 0.47) were significantly lower in SLE-APS patients compared to that in controls.	Cross-sectional 5

(*continued*)

Table 4 (*Continued*)

Study	Number of cases/controls (mean age in years)	Main findings	Study type and Quality assessment (NOS)
		The frequency of oligo/azoospermia was significantly higher in SLE-APS patients (40 vs. 0%, $p = 0.007$).	
Spondyloarthropathies			
Ramonda [55] Italy	Cases: 10 (28.7 ± 8.6) Controls: 20 (27.4 ± 4.2)	Semen analysis highlighted a significant reduction in the percentage of progressive and non-progressive motile sperm in patients compared with control subjects (p=<0.05). Two inverse Spearman correlations were detected: • CRP and percentage of sperm with normal morphology ($P = 0.026$; r=−0.0728). • DAS-28 and overall motility ($p = 0.048$; r= −0.949). The other sperm parameters and the percentage of sperm aneuploidies in the SpA patients did not show significant differences.	Case-control 4
Nukumizu [58] Brazil	Cases: 20 (33) Controls: 24 (28.5)	AS patients and controls had normal external genitalia. Sperm analysis was comparable in both groups. Varicocele was found in 40% of AS patients compared to 8% of healthy controls and this finding was associated with sperm abnormalities ($p = 0.175$).	Cross-sectional 4
Micu [57] Norway	Cases: 23 (34.7) Controls: 42 (34.8)	Sperm quality in patients with active AS was comparable to sperm quality in healthy controls.	Case-control 4
Villiger [59] Switzerland	Cases: 26 (30) Controls: 102 (35)	Impaired sperm quality was especially found in AS patients without TNF-inhibitors and active disease: Sperm abnormalities were found in 10/11 patients without TNF-inhibitor therapy. • Sperm of these 11 patients had significantly poorer motility ($p = 0.001$) and vitality ($p = 0.001$) compared to 15 patients tested during longstanding TNF-inhibitor therapy.	Cross-sectional 4
Uzunaslan [61] Turkey	Cases: 79 (38.3) Controls: 43 (42)	Higher infertility rate after diagnosis in AS patients was reported (9.1%) but this was not significant compared to healthy controls (2.9%), $p = 0.502$. AS patients had significantly fewer children when compared with other groups ($p = 0.013$): • AS: 1.9 • BS: 2.3 • Familial Mediterranean Fever (FMF): 2.4 • Healthy controls: 2.4	Case- control 3
Systemic sclerosis			
Hong [68] Canada & USA	Cases: 48(52 ± 1.7) Controls: 55 (53 ± 2.3)* *Controls: RA patients	Patients with SSc had significantly y lower number of biological children than patients with RA (2.0 ± 0.2 vs 2.7 ± 0.2, p=<0.01). Men with RP fewer children than men without RP (2.0 ± 0.2 vs 2.6 ± 0.2, p=<0.02).	Case-control 3
Bechet's syndrome			
Cetinel[74] Turkey	Cases: 104(40) Controls: 31 (29)	The frequency of epididymitis was significantly higher in patients with BS than controls (19.2 vs 0%, $p = 0.001$). The frequency of infertility was higher in patients with BS than controls (9.6 vs 2.3%, p=NA).	Case-control 5
Uzunaslan[61] Turkey	Cases: 162 (39) Controls: 43 (42)	Higher infertility rate after diagnosis in AS patients was reported (BS with major organ involvement 7.95% and BS without major organ involvement 10.2%) but this was not significant compared to healthy controls (2.9%, $p = 0.502$) • 17.7 of male patients with BD was considered to have compromised fertility and among them the most common etiology was varicocele. The average number of children (2.3), miscarriages (0.4) and of children born with congenital abnormalities (4.4) was similar to controls.	Case-control 4
Auger [76] France	Cases: 68 (28) Controls: 1448 (NA)	66.7% of patients with BS were considered normozoospermic. Differences in the sperm concentration, count, motility and morphology were significant when comparing data to healthy controls.	Case-control 5

Table 5
Summary of pregnancy and offspring outcomes.

Study	Patients/controls	Findings	Quality assessment
Rheumatoid arthritis			
Rom [24] Denmark	NA	Among 1086 born children exposed to paternal RA: • No statistically significant associations were found with indicators of fetal growth, preterm birth compared to the general population.	Cohort 8
Wallenius [23] Norway	NA	Among 2777 births from 1796 men with RA: • Relative risks from serious malformation were not different between DMARD exposed and non-exposed group. • Birth weight was not different between groups.	Cohort 6
Bechet syndrome			
Uzunaslan [61] Turkey	Cases: 162 (39) Controls: 43 (42)	The number of infants with congenital anomalies was not increased among patients with BS when compared with other groups.	Case-control 4

age-matched healthy controls (20.6 [standard deviation 4.04] vs 29.21 [standard deviation 0.750] p=<0.001). Scores of 26 or higher were considered as normal sexual function. Lower IIEF scores were associated with higher depression scores. No association between ED and medication use or the presence of oral and genital ulcers was found [71].

The association between ED and depression in patients with BS was further investigated by Gul et al. in a study of 24 BS male patients (mean age 35.8 years). They reported that SD was significantly more prevalent in BS than in controls (80 vs 32%, p = 0.001). This was associated with higher depression scores. Male patients with BS were found to have more problems in the following areas: impotence, premature ejaculation and sexual satisfaction [72]. Similar findings were reported by Batmaz et al. in a group of 72 sexually active male BS patients (mean age 36.5 years) [73].

Fertility

Cetinel et al. sent questionnaires to 104 male patients with BS (mean age 31 years) to screen for urologic manifestations and found a significantly high frequency of epididymitis in patients with BS compared to controls (19.2 vs 0%, p = 0.001). They also found a higher incidence of infertility and varicocelectomy in BS patients, but the difference was not statistically significant compared to healthy controls [74].

The incidence of varicocele was also increased in BS in a study that included 47 patients with BS (mean age 23.4 ± 3.2 years) and 31 age-matched healthy controls. Scrotal pain or a palpable mass was detected by physical examination in 24 (51.1%) BS patients and in 5 (16%) healthy controls (p = 0.002). No sperm analysis was performed in these patients [75].

A large study that included 162 male patients with BS, compared fertility rates among them and patients with other rheumatic diseases (AS, Familiar Mediterranean Fever (FMF)) and healthy controls). Interestingly, a trend for an increased rate of infertility (defined as the inability to conceive after 1 year of unprotected intercourse) after diagnosis was found in all the groups with rheumatic diseases (BS: 9%, FMF: 7.5% and AS 9.1%) but this was not significant compared to the rate seen in healthy controls (2.9%) (p = 0.404). With the exemption of AS, the average number of children was similar among groups [61].

In the only identified study that investigated semen quality in BS patients, Auger et al. using sperm banking data compared the sperm characteristics of BS patients and healthy fertile men. Moderate alterations in semen quality were observed. Of particular interest, the authors reported that sperm alterations were present even before treatment and this might be related to disease-related factors [76].

Reproductive hormones

No articles were included.

Pregnancy and offspring outcomes

The average number of miscarriages and the percentage of infants born with congenital anomalies were not increased in children fathered by patients with major organ BS when compared with healthy controls (0.429 vs 0.398 and 4.49 vs 4.85%, respectively) [61].

Other rheumatic diseases

Sarcoidosis

In a study that included 30 patients diagnosed with sarcoidosis (mean age 43.6 years), Spruit et al. found that sarcoidosis patients were more likely to have lower median free testosterone concentrations than 26 age-matched healthy controls [7.32 (5.48–8.72) vs 9.25 (7.54–9.87) ng/dl, p = 0.0062] [77].

Azoospermia, teratozoospermia and oligospermia were frequent findings in case reports of patients with sarcoidosis [78–86]. Treatment with corticosteroids improved semen quality in some cases [79,80,86,87]. Granulomas were also reported in testicles and epididymis of patients with sarcoidosis [88–92].

Vasculitis

Hypogonadism was reported in 10 out of 19 (52.6%) male patients diagnosed with Granulomatosis with Polyangiitis (GPA) (mean age 58.4 years) compared to 0 out of 38 age-matched controls (p=<0.001). No correlation with clinical factors or current/past medication use was found. Authors concluded that a subclinical involvement of the testes in GPA patients was possible [93].

Androgen deficiency and its association with fatigue were analyzed in a study that included 70 male patients with ANCA-associated vasculitis (mean age 59 years). A high prevalence of androgen deficiency among these patients was reported (47%) and testosterone levels were associated with physical functioning and fatigue [94].

Pregnancy outcomes among partners of male patients with vasculitis were analyzed by Clowse et al. Data from 107 patients were reported, 54 men reported conceiving 157 pregnancies. Pregnancy loss rate was not significantly higher among pregnancies conceived following a diagnosis of vasculitis (n = 139) compared to those prior to diagnosis (n = 18) (41.2% vs 23%; relative risk 2.34 [CI95% 0.71 – 7.70], p = 0.16) [95].

Autoinflammatory syndromes

Azoospermia due to testicular amyloidosis in a patient with FMF, confirmed with a testicular biopsy, was reported [96]. Fever was shown to drastically reduce sperm output and this was accompanied by an increase in the percentage of abnormal spermatozoa in a study conducted by French et al.[97]

The rate of abortions was comparable in 222 pregnancies among 60 partners of male patients diagnosed with FMF (7%) and 788 pregnancies among 230 healthy women married to healthy men (16%) [98].

A small retrospective study from France reviewed the medical records of all male patients diagnosed with Muckle-Wells syndrome (MWS) and NLRP3 mutations founding that 6 out of 9 patients were unable to conceive a pregnancy despite regular sexual activity during at least 2 years and that sperm quality was abnormal in 88% of the samples obtained. Multiple mechanisms were discussed as possible causes for this association, such as recurrent fever episodes, excessive amounts of IL-1B and IL-18 [99].

Autoimmune diseases in general

Retrospective cohort studies from the United States have reported an increased risk of developing any rheumatic disease in patients diagnosed with hypogonadism and infertility. Among 123,460 males diagnosed with hypogonadism (mean age 46.5 years) and 370,380 age-matched males not diagnosed with hypogonadism multivariable analysis showed that untreated hypogonadism was associated with an increased risk of developing any rheumatic autoimmune diseases (3.2 versus 2.2%; HR = 1.33, 95% CI = 1.41, 1.52) [100]. Using the same database, Brubaker et al. reported a higher risk of developing RA and general immune disorders, like SLE, (HR 1.56, 95% CI 1.19–2.05 and HR 3.11, CI95% 2.00–4.86, respectively) among 33,077 infertile men (mean age 33 years) compared to 77,693 age-matched vasectomized men [101].

Discussion

Summary of evidence

Sexual function

Our study found that male patients with rheumatic diseases have a high prevalence of SD; this was statistically significant in many studies when comparing patients with rheumatic diseases to age-matched healthy controls. In addition, SD seems to occur at a younger age in patients with rheumatic diseases. For comparison, in a

multicenter study that included data from 27,839 adult men (aged 20–75 years), the overall self-reported prevalence of SD was 16% and it ranged from 8% in men aged 20–29 years to 37% in men aged 70–75 years [102].

Recently, the EULAR published recommendations on screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases [103]. As it is the case for these comorbidities (i.e. cardiovascular disease, infections and depression), SD can represent an important burden to male patients and contribute to a lower quality of life. Most of these patients remain undiagnosed and uninformed about SD. We encourage rheumatologists to talk about sexual health with their patients. The use of widely available screening tools and early referrals to specialists should be considered in men with rheumatic diseases and SD, especially those trying to conceive. For clinical practice and future research projects in this topic, we recommend the use of validated screening tools (I.E. IIEF for sexual dysfunction).

Rheumatic diseases can affect several organs via factors like systemic inflammation in RA and SLE and fibrosis in SSc. These factors have been shown to be associated with the increased prevalence of SD in men with rheumatic diseases. A link between RA-induced inflammation and cardiovascular disease is already known and has been widely studied. Based on our SR findings, it is plausible that a similar link between RA-induced inflammation and the development of SD exists and that it could be an early sign of endothelial dysfunction. In addition to the classical factors associated with SD such as older age, depression and anxiety, this link could also play an important role in the pathogenesis of SD in men with rheumatic diseases

In conclusion, SD is a common problem in male patients with rheumatic diseases. This association might result from the fact that several key factors contribute to the etiopathogenesis of rheumatic diseases and SD.

Reproductive hormones

A clear effect of rheumatic diseases on the pituitary-testicular axis exists. Hypogonadism and testicular dysfunction was a common finding, especially in patients with RA and SLE and this was associated with disease activity. Especially in patients with SLE, differentiating between primary (Klinefelter Syndrome, drug toxicity) and secondary hypogonadism (inflammation) should be considered in future research projects and in the clinic.

Interestingly, when comparing the androgenic status of men with RA and AS, a rheumatic disease that is more prevalent in men than women, it was found that only RA had a detrimental effect on testicular function. It is possible that based on different inflammatory phenotypes, disease activity in RA and SLE can result in testicular damage via different mechanisms.

Fertility

Infertility affects 10–15% of men in their prime reproductive age and the cornerstone of laboratory evaluation of infertile men is a conventional semen analysis [104]. Semen quality in men with rheumatic diseases can be impaired in patients with SLE, SpA, sarcoidosis, BD and MWS. Sperm count and motility were the most common semen quality parameters affected. Systemic inflammation can cause impaired spermatogenesis by mechanisms that have not been described yet.

Varicocele, one of the most common 'reversible' causes of infertility in the general population, can be present in more than half of men with AS and to a lesser extent in BS. Rheumatologists should be aware of this association and actively screen it in every AS/BS patient with a wish to conceive. We also encourage researchers to take this association into account when studying semen quality of male patients with AS (and other rheumatic diseases), since we believe that some of the findings regarding impaired semen quality could be associated with non-identified varicocele and not to the disease itself or as a side effect of therapy.

Unexplained subfertility is a common problem in women with RA [105] but fertility status in men with rheumatic diseases has not been extensively studied. Men with AS, SLE and SSc had a lower number of children than controls in small studies, nevertheless, since many factors that might contribute to these findings such as voluntary childlessness (related or unrelated to the diagnosis of a rheumatic disease) were not reported, larger epidemiological studies that take these factors into account are needed to verify this association.

Since conventional semen analysis can be normal in infertile patients, DFI might be a better marker for infertility in men with SLE and other rheumatic diseases. More studies are needed to make recommendations on the use of DFI in this population.

Pregnancy and offspring outcomes

The information regarding the influence of paternal RA and vasculitis on pregnancy outcomes is based on a few studies. We found no evidence pointing towards a negative effect of paternal RA and vasculitis on pregnancy outcomes. Unfortunately, there is no information about pregnancy outcomes in partners of male patients with other rheumatic diseases and over the impact of paternal disease on offspring's outcomes.

Conclusion

"A systemic disease is one that affects a number of organs and tissues, or affects the body as a whole" [106]. The collaboration between multiple organs is needed to achieve full male sexual health and it is now evident that many of these organs can suffer detrimental effects secondary to rheumatic diseases. Rheumatic diseases and male sexual health should not be considered anymore as being unrelated conditions.

Unfortunately, several limitations should be addressed; most of the studies included small numbers of patients and controls. In addition, studies about sexual function and fertility in men with rheumatic diseases suffer from inconsistent methodological quality, definitions of sexual dysfunction varied in several studies, a wide variety of screening questionnaires and/or diagnostic tools were used, relevant comorbidities that can also have a direct effect on sexual function such as depression were not reported in all studies and results might only apply to the specific populations studied.

More and better research is needed to fully understand the effect of rheumatic diseases in male sexual health. Epidemiological, clinical and basic science studies are needed and should be done in such a way that results can be comparable in different populations. For this reason, for future research we strongly advice on the use of standardized methods and definitions. Collaboration between rheumatologists, andrologists and other experts on this topic is encouraged.

We also encourage rheumatologists and other clinicians taking care of men with rheumatic diseases to consider male sexual health in their clinical practice. Timely detection and treatment of SD and fertility problems can have a big impact on the quality of life of patients and avoid the use of expensive medical care. To achieve this, rheumatologists and patients must have the opportunity and the necessary tools to discuss this topic.

We conclude that male sexual and reproductive health is affected by rheumatic diseases, the degree and extent of this is still unknown and varies per disease. More research is needed and rheumatologists should address this topic with their patients.

Declaration of Competing Interest

None.

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Supplementary materials

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