

AUTOIMMUNE DISEASES AND MALE FERTILITY: A SYSTEMATIC REVIEW

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ΕΥΧΑΡΙΣΤΙΕΣ

Με την ολοκλήρωση της μεταπτυχιακής διπλωματικής μου εργασίας, θα ήθελα να εκφράσω τις θερμές μου ευχαριστίες σε όλους όσους συνέβαλλαν στην εκπόνησή της.

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ΠΕΡΙΕΧΟΜΕΝΑ

1. Περίληψη	4
2. Γενικό μέρος	5
3. Σκοπός μελέτης	6
4. Μεθοδολογία	8
5. Στατιστική ανάλυση	7
6. Αποτελέσματα	8
7. Συζήτηση	20
8. Βιβλιογραφία	23

ΠΕΡΙΛΗΨΗ

Κατά την διάρκεια των τελευταίων χρόνων νέες στοχευμένες θεραπείες έχουν αναπτυχθεί για την αντιμετώπιση των αυτοάνοσων νοσημάτων. Παρά ταύτα η γονιμότητα των ανδρών με αυτοάνοσα νοσήματα φαίνεται να επηρεάζεται είτε από την ίδια την νόσο είτε από την εκάστοτε αγωγή που χρησιμοποιείται. Η συγκεκριμένη εργασία συνοψίζοντας τριάντα εννέα άρθρα της παγκόσμιας βιβλιογραφίας τα οποία σχετίζονται την ανδρική υπογονιμότητα με δέκα αυτοάνοσα νοσήματα (συστηματικός ερυθματώδης λύκος, δερματομυοσίτιδα, κοιλιοκάκη, ουρική αρθρίτιδα, ρευματοειδής αρθρίτιδα, σαρκοείδωση, φλεγμονώδεις νόσοι του εντέρου, αγκυλοποιητική σπονδυλίτιδα, νόσος Behcet και ψωρίαση) επιχειρεί να αποκαλύψει την συνδεσή τους με την ανδρική υπογονιμότητα.

SUMMARY

During the last years new targeted regimen for several autoimmune diseases has been developed leading to an ameliorated quality of life for these patients. Nevertheless, their fertility potential seems to be impaired either by the activity of the autoimmune diseases or by the medical treatment used to suppress these conditions. A search of English-language articles from electronic databases was conducted for this paper. The results that were used referred to impaired fertility in male patients with systemic lupus erythematosus, Behcet's disease, gout, dermatomyositis, celiac disease, rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, psoriasis and sarcoidosis. This systematic review intends to reveal how autoimmune diseases and their regimen affect male fertility.

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ABSTRACT

Background: During the last years new targeted regimen for several autoimmune diseases has been developed leading to an ameliorated quality of life for these patients. Nevertheless, their fertility potential seems to be impaired either by the activity of the autoimmune diseases or by the medical treatment used to suppress these conditions. This systematic review intends to reveal how autoimmune diseases and their regimen affect male fertility.

Materials and methods: A search of English-language articles from electronic databases was conducted. The results that were used referred to impaired fertility in male patients with systemic lupus erythematosus, Behcet's disease, gout, dermatomyositis, celiac disease, rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, psoriasis and sarcoidosis.

Results: Thirty nine articles were finally included regarding the following diseases: dermatomyositis (1), systemic lupus erythematosus (8), Behcet's disease (3), gout (1), celiac disease (2), rheumatoid arthritis(5), ankylosing spondylitis(5), inflammatory bowel disease (5), psoriasis (4), sarcoidosis (3) as well as two systematic reviews. Cyclophosphamide therapy seems to impair fertility in male patients with systemic lupus erythematosus and Behcet's disease. Colchicine use may lead to sperm abnormalities in patients with gout whereas anti-TNFtreatment in ankylosing spondylitis does not affect the fertility potential. Antisperm antibodies and sulphasalazinetreatment in rheumatoid arthritis as well as mesalazine, infliximab and methotrexate use in inflammatory bowel disease result in gonadal dysfunction, respectively. More data addressing male fertility are needed for patients with dermatomyositis, sarcoidosis, psoriasis and celiac disease.

Conclusions: Fertility impairment is common in autoimmune diseases. Henceforth, more studies are needed in order to identify the relationship between fertility and immunity.

INTRODUCTION

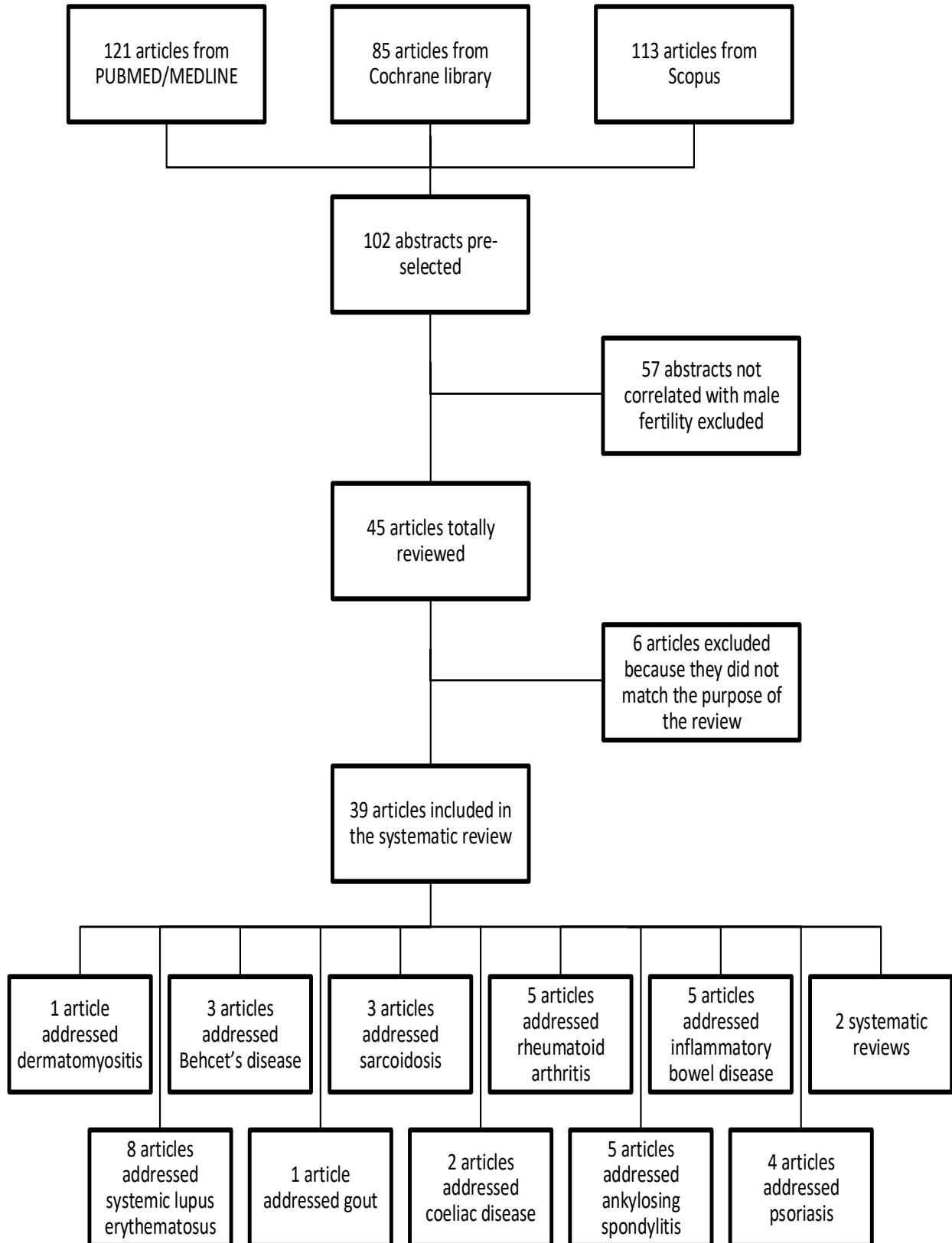
Recent estimations have reached to the point that approximately 7.6%-9.4% of the global population suffer from autoimmune diseases (1). Researchers have also identified several comorbidities associated with autoimmune diseases that affect several systems (2).

Decreased fertility in women under regimen for rheumatic diseases has been indicated by several publications. This impairment is caused either directly by the inflammation provoked by the autoimmune disease or as a side effect of its drug treatment (3).

Several treatments, especially alkylating agents such as cyclophosphamide, have been directly correlated with irreversible infertility in both men and women (4). However, new targeted therapies like monoclonal antibodies promise better results and fewer side effects for patients including fertility parameters (5)

The impact of autoimmunity on male patients has been poorly investigated. The papers reviewed in this publication have evaluated hormone profiles, semen analyses and physical examinations of male patients under several regimens for autoimmune diseases.

This systematic review aims to reveal the contributing factors of infertility in men with autoimmunity disorders and suggest potential regimen alterations that could lead to optimum fertility outcomes.



Search and selection

A search of English-language articles listed in the electronic databases of SCOPUS, PUBMED/MEDLINE and Cochrane Library was conducted. The following terms were used: inflammatory bowel disease >, < Crohn's disease >, < ulcerative colitis >, < psoriasis >, < rheumatoid arthritis >,< sarcoidosis >, < systematic lupus erythematosus >, <ankylosing spondylitis >,<Behcet's disease >,< celiac disease >, < dermatomyositis >,< gout >,< male infertility >, < sperm quality >,< semen quality >, < sperm > and < fertility impairment >.

The search was performed in English language and only English language papers were selected. Their abstracts were evaluated to determine whether they match or not the study's objective. Case control studies, systematic reviews and randomized control trials were included. Moreover, they referred to hospital or population-based studies about fertility in male patients with AS,BD, CD, DM, Gout, IBD, Psoriasis, RA, SLE and Sarcoidosis, (Figure 1)

Systemic lupus erythematosus

Eight publications were selected to investigate the connection between systemic lupus erythematosus and male infertility (Table 1). There were two papers that assessed the sperm abnormalities and the penile alterations in those patients (6,7). Both of them revealed lower median sperm concentration, percentages of sperm motility and normal sperm forms. Moreover, they identified IV treatment with cyclophosphamide as the major factor of these alterations.

Another review of 2004 evaluated the gonadal toxicity of patients with lupus nephritis on cyclophosphamide regimen showing a clear relation between the duration of the regimen and azoospermia (8). As it was concluded, the risks are dependent on the age of the patient as well as on the cumulative dose of cyclophosphamide, showing a possible lead to azoospermia. On the other hand, Niaki's review supported that additional studies are required to explore the impact of systemic lupus erythematosus on male fertility, although proving also the dose dependent gonadotoxicity with IV cyclophosphamide (9).

Twenty-five male SLE patients and 25 healthy controls underwent urologic evaluation and semen analysis in 2009 identifying higher frequencies of gonadal dysfunction parameters (increased FSH, increased LH, sperm abnormalities) and commoner erectile dysfunction incidents in the first group (10).

Suehiro's paper extrapolated a higher frequency of testicular Sertoli cell dysfunction associated with semen abnormalities in thirty-four SLE patients who underwent evaluation of serum inhibin B (11). Moreover, the study identified a higher dysfunction in patients with lower serum inhibin B. Thirty-five SLE patients showed a higher prevalence of sperm abnormalities

associated with reduced testicular volume in Soares review after being subjected to urologic evaluation, semen analysis and Doppler u/s (12).

The last study of Silva referred to four patients with juvenile onset systemic lupus erythematosus who underwent clinical and laboratory evaluation. One of the four patients showed high FSH and LH levels and all patients had abnormal sperm evaluations (13).

Table 1- Systemic lupus erythematosus and male infertility

Author	Year	Study population	Results	Conclusion
Rabelo-Junior CN (6)	2013	10 patients with SLE-APS and 20 healthy controls	SLE-APS patients had lower sperm concentration, sperm motility and normal sperm forms	Gonadal dysfunction in SLE-APS patients possibly caused by IV CYC
Polyanna Maria F. Soares (7)	2007	35 patients with SLE and 35 healthy controls	SLE patients had higher sperm abnormalities and reduced testicular volume	Gonadal dysfunction possibly caused by IV CYC
J.F.M Wetzels (8)	2004	Patients with lupus nephritis (review from several papers)	Risk of azoospermia particularly of cumulative dosage above 300 mg/kg	The risks are dependent on the age of the patient and on the cumulative dose of CYC. Patients should be advised of the risk of permanent infertility
Omid Zahedi Niaki (9)	2017	SLE patients(review from several papers)	Drugs used for SLE, especially IV CYC, are associated with direct testicular damage	Drugs used for SLE, especially high doses of IV CYC, may avert irreversible infertility but additional studies are required
Cloris Artis Almeida da Silva (10)	2009	25 SLE patients and 25 healthy controls	Higher frequencies of erectile dysfunction (20%) and sperm abnormalities (48%) as well as elevated levels of FSH and LH)	Identification of erectile and gonadal dysfunction in male SLE patients

Author	Year	Study population	Results	Conclusion
Suehiro (11)	2008	34 SLE patients subdivided into two groups (group 1 = low serum inhibin B and group 2= normal serum inhibin B)	Sperm concentration and sperm count were lower in group 1 while FSH and LH levels were higher in that group	High frequency of testicular Sertoli cell dysfunction in male SLE patients
Soares (12)	2007	35 SLE patients underwent urologic evaluation, Doppler u/s and semen analysis	Low sperm count, low sperm volume and high prevalence of sperm alterations	SLE patients have a high frequency of sperm abnormalities. IV CYC is the major factor of potential damage
Silva CA (13)	2002	4 men with juvenile onset SLE underwent clinical and laboratory evaluation	Anti-sperm antibodies negative in all patients, abnormal semen evaluations in all patients, one patient showed high FSH and LH levels	Decreased fertility of men with juvenile onset SLE based on sperm abnormalities

Note:SLE= systemic lupus erythematosus, **APS** = antiphospholipid syndrome, **IV**= intra venus,CYC= cyclophosphamide, **FSH**= follicle-stimulating hormone, **LH**= luteinizing hormone,**u/s**= ultrasound

Behcet disease

There were three publications about the correlation between the use of cyclophosphamide and colchicine for Behcet disease and male infertility. Fukutani evaluated the reproductive function of 31 adult male patients with Behcet disease during their treatment with cyclophosphamide and/or colchicines (14). The report reached to the conclusion that patients who received cyclophosphamide had higher rates of azoospermia as long as elevated follicle-stimulating hormone levels. On the contrary, no seminal or hormonal parameters changes were observed in patients treated only with colchicine.

In 1995 62 male patients treated with colchicine for Behcet’s disease were evaluated for infertility. After sperm analysis and penile colour flow Doppler sonography oligonecrospermia and arterial insufficiency was revealed in approximately one third of the patients (15).

On the other hand, Haimov-Kochman doubts the link between colchicine and male infertility implying that the sperm pathology is caused by the underlying disease (16).

Table 2 – Behcet’s disease and male infertility

Author	Year	Study population	Results	Conclusion
Fukutani (14)	1981	31 male patients with BD under CYC and/or colchicine treatment	Azoospermia or severe oligospermia in 13 of 17 patients receiving CYC with or without colchicine. FSH levels were higher in CYC treated patients	CYC may impair spermatogenesis in adult men whereas colchicine does not
Sarica K (15)	1995	62 male patients under colchicine therapy for BD	37.1% of patients had oligonecrospermia and 3.2% had azoospermia	Urologic manifestations of BD and possible adverse effects of colchicine should be carefully monitored
Haimov-Kochman R (16)	1998	Patients with Gouty arthritis or FMF or BD	Spectrum of pathology from oligospermia to normospermia with disturbances in sperm motility	Colchicine by itself may not have a significant adverse effect on sperm production and function

Note: BD= Behcet’s disease, CYC= cyclophosphamide, FSH= follicle-stimulating hormone, FMF= familial Mediterranean fever

Gout

There is one case report regarding the correlation of male infertility and the use of colchicine for gout disease. One male partner with mild gouty arthritis treated with colchicine underwent sperm analysis and FISH with specific probes for chromosomes 18, X and Y during in vitro fertilization attempt (17). Results revealed that 11% of the spermatozoa displayed a normal morphology and that 2.3% of the sperm cells were classified as aneuploid and that 1.3% of the abnormal sperm nuclei were nullisomic for either chromosome X or Y. The report concluded that some men are unusually sensitive to a toxic effect of colchicine which is capable of inducing chromosomal abnormalities.

Dermatomyositis

One publication regarding male infertility in patients with juvenile dermatomyositis was used (18). In this study there were initially 18 males with juvenile dermatomyositis and 5 controls of the same age. The five post-pubertal patients with juvenile dermatomyositis were compared with the healthy controls on the basis of semen analyses, urologic evaluation, testicular Doppler ultrasound as well as hormone profile. All patients had teratozoospermia and one of the patients with cutaneous active disease had anti-sperm antibodies. In addition, one of the patients who was treated with a high dose of intravenous cyclophosphamide had oligoasthenoteratozoospermia which was

normalized five years after the treatment's interruption.

Table 3 – Gout, dermatomyositis and male fertility

Author	Year	Study population	Results	Conclusion
Kastrop P. (17)	1999	Two infertile males who were treated with colchicine underwent sperm analysis and FISH	11% of the spermatozoa displayed a normal morphology, 2.3% of the sperm cells were aneuploid and 1.3% of the abnormal sperm nuclei were nullisomic for X or Y	Some patients are unusually sensitive to the toxic effect of colchicine
Moraes (18)	2008	18 males with juvenile dermatomyositis and 5 age-matched controls	All patients had teratozoospermia and one, treated with IV CYC, had oligoasthenoteratozoospermia	Serial semen analyses in study larger populations are necessary to identify the correlation between DM and male infertility

Note:FISH= fluorescence in situ hybridization, **IV**= intra venus, **CYC**= cyclophosphamide, **DM**= deratomyositis

Coeliac disease

Two papers addressing coeliac disease and its relationship with male fertility were studied. Farthing in 1983 compared 39 men with treated and untreated coeliac disease with 19 men with Crohn's disease of similar age (19). This study reached to the point that there is a derangement of pituitary regulation of gonadal function in men with coeliac disease, as exaggerated

responses of FSH and LH to LHRH were found in the majority of the patients studied. A recent Swedish cohort study of 7.121 men with coeliac disease, verified with duodenal-jejunal biopsy, found a normal fertility in men with celiac disease as the overall fertility hazard ratio in men was 1.01 (20).

Table 4- Coeliac disease male fertility

Author	Year	Study population	Results	Conclusion
Farthing MJ (19)	1983	39 men with treated and untreated CD and a control group of 19 men with Crohn's disease	LH levels were increased in 53% , FSH in 26% and serum prolactin in 25% of the untreated CD patients	There is a derangement of pituitary regulation of gonadal function in men with CD
Zugna D (20)	2011	7121 men with CD compared with 31671 age-matched male controls	The fertility hazard ratio in men with biopsy-verified CD was 1.01 (95% confidence interval 0.99-1.04)	Normal fertility in men diagnosed with CD

Note:CD= coeliac disease, **FSH**= follicle-stimulating hormone, **LH**= luteinizing hormone

Rheumatoid arthritis

Five publications selected focused on the aspects of male fertility in rheumatoid arthritis. A study of 2017 suggested that patients treated with methotrexate for rheumatoid arthritis must be counselled of discontinuation prior to conception as well as of sperm cryopreservation (21). On the other hand, French’s study showed no reports of adverse pregnancy outcomes among the partners of men exposed to methotrexate for over six months (22).

A big study of the effects of paternal exposure to anti-rheumatic drugs found no statistically significant association between their use and congenital malformations or adverse pregnancy outcomes (23). However it was implied that some drugs like sulphasalazine may impair male fertility. Gordon evaluated the hormonal profiles of patients with rheumatoid arthritis revealing a decrease in testosterone levels and an increase in FSH and LH levels (24) and a paper of 2008 after studying 32 men with rheumatoid arthritis reached to the conclusion that antisperm antibodies may be induced by the disease and consequently may affect male fertility (25).

Table 5- Rheumatoid arthritis and male fertility

Author	Year	Study population	Results	Conclusion
Guttierez JC (21)	2017	RA patients of reproductive age under MTX treatment	MTX may have an impact on paternal-mediated teratogenicity	Patients treated with MTX must be counselled on the likelihood of its adverse effects and on the role of sperm cryopreservation
French AE (22)	2003	Male patients with psoriatic arthritis and RA under MTX treatment	Some cased reports showed no effect and some reversible sterility	More studies are needed to determine the role of MTX on male fertility
Chiara Bazzani (23)	2014	Male patients with chronic arthritis under several antirheumatic drugs	Sulphasalazine may impair male fertility but overall no statistically significant association was revealed	New multicentric prospective studies are needed
Gordon (24)	1986	31 patients with RA and 95 normal controls	Higher levels of FSH and LH as well as lower levels of testosterone	Testicular damage may be caused by disease activity
Shirashi (25)	2008	32 men with RA and 80 healthy controls	3% of RA patients had antisperm antibodies	Antisperm antibodies possibly elevated by RA and may affect male fertility

Note:RA= rheumatoid arthritis, **MTX**= methotrexate, **FSH**= follicle-stimulating hormone, **LH**= luteinizing hormone

Ankylosing spondilitis

Five publications assessed male fertility on patients with alkylosing spondylitis. The major points of each publication have been summarised in Table 6. A case report of a 36-year-old infertile patient revealed a high incidence of headneck and tale abnormalities as well as the presence of immature sperm forms (26). In 2014 a comparison between 25 AS patients, after 3-6 months of TNF-a therapy, and 42 controls showed no statistically significant difference in sperm quality (27). The possible effect of anti-TNF therapy in patients with AS was also

investigated in 2013 regarding sex hormone levels, inhibin B levels seminal analysis reaching the same outcome(28).

A publication of four AS patients treated with infliximab reached to the conclusion that there is no association between its use and infertility issues as all patients fathered at least one child (29). On the other hand, varicocele as a factor of fertility impairment was implied by a study of 2012 as 40% of the included AS patients developed varicocele which is apparently associated with teratospermia (30).

Table 6- Ankylosing spondylitis and male fertility

Author	Year	Study population	Results	Conclusion
Chazimeletiou (26)	2018	One patient	Headneck and tale abnormalities/immature sperm forms	AS may affect male fertility
Micou (27)	2014	23 AS patients and 42 controls	No statistically significant difference in sperm quality	Sperm quality was not affected by TNF-a therapy
Almeida (28)	2013	20 AS patients and 24 controls	Normal sex hormone and inhibin B levels	Normal testicular Sertoli cell function in AS patients under TNF-a therapy
Paschou (29)	2009	4 AS patients treated with infliximab	All patients had at least one child	Infliximab is not associate with infertility issues
Nukumizu (30)	2012	20 patients with AS and 24 controls	40% of AS patients had varicocele	Possible interrelation between AS and varicocele may lead to fertility impairment

Note:AS= ankylosing spondylitis, TNF-a= tumor necrosis factor-a

Inflammatory bowel disease

Five publications regarding the association between inflammatory bowel disease and male infertility were selected. A study of 2017 e revealed better sperm concentration and motility in men treated with anti-tumor necrosis factors than those who were on another regimen (31). The same study indicated lower sperm concentration in Crohn’s disease patients than ulcerative colitis patients. Shin’s paper evaluated the sperm parameters of seven men with IBD before and after discontinuation of mesalazine during fertility treatment showing an increase of sperm motility, semen volume and normal sperm forms (32).

A crossover-crossback prospective study brought attention to possible side-effects of exposure to high dibutyl-phthalate mesalazine as the men studied had decreased sperm motility and sperm count even after crossback to non dibutyl-phthalatemesalazine (35). A recent study evaluated the fertility outcome of ten men treated with infliximab reporting lower normal oval forms as well as impaired sperm motility (33). Finally, a case-control study of 2018 investigated the effects of methotrexate on sperm quality reaching to the point that methotrexate may lead to DNA fragmentation and vast cell damage due to oxidative stress (34).

Table 7- Inflammatory bowel disease and male fertility

Author	Year	Study population	Results	Conclusion
Valer P (31)	2017	Men with IBD and control subjects	Lower sperm concentrations and sperm motility in patients with Crohn's disease. Patients under anti-TNF treatment showed better motility and morphology. No significant differences were found between IBD patients and controls	Men with Crohn's disease had poorer semen quality than those with ulcerative colitis. Treatment with anti-TNF drugs does not seem to be associated with sperm quality
Shin T (32)	2014	1225 male subfertile patients with IBD who ceased mesalazine	Sperm motility and sperm count were significantly improved after the discontinuation of mesalazine	More studies are needed to identify the relationship between male fertility and mesalazine

Mehadevan U (33)	2005	10 patients with IBD under infliximab treatment	Decreased sperm motility and normal oval forms after infliximab infusion	Infliximab therapy may decrease sperm motility and the number of normal oval forms
Ley D (34)	2018	7 men exposed to MTX for at least 3 months and 1912 age-matched controls	Significant increases in levels of DNA fragmentation and damage from oxidative stress in IBD patients	MTX may induce integrity in sperm and cause damage via oxidative stress
Nassan FL (35)	2016	73 men with IBD taking mesalamine (group 1= men taking non-DBP containing mesalamine at baseline and group 2=men taking high-DBP containing mesalamine at baseline)	Group 1 patients had a decrease of total sperm motility and motile sperm count	Men newly exposed to high-DBP mesalamine showed a reduction in several semen parameters

Note: IBD= inflammatory bowel disease, TNF= tumor necrosis factor, MTX= methotrexate, DNA= deoxyribonucleic acid, DBP= dibutyl phthalate

Psoriasis

There were four papers addressing psoriasis and its relationship with male fertility. A study of 2017 compared 50 psoriatic patients with 50 controls using semen analysis as well as andrological examination. Lower testosterone and sex hormone binding globulin levels in addition to inflammation of the accessory glands were observed in psoriatic patients (36). Heppt’s prospective study of 2017 revealed increased sperm abnormalities and indications of genital tract infection in patients treated with tumor necrosis factor – alpha inhibitors (37). However, the study observed no negative side- effects on the sperm quality of the treated patients. A paper of 1977 failed to reveal a correlation between the use of methotrexate and topical corticosteroids sperm quality as those were attributed to psoriatic lesions in the genital tract (38). Furthermore, the study of Hui Liu investigated the effect of different doses of

acitretin, both before and after treatment, on sperm parameters finding no significant difference than the healthy control individuals (39).

Table 8- Psoriasis and male fertility

Author	Year	Study population	Results	Conclusion
Caldarola G (36)	2017	50 male psoriatic patients and 50 healthy age-matched controls	Lower testosterone and SHBG levels as well as decreased sperm motility in psoriatic patients. Inflammation of the accessory glands in 35/50 psoriatic patients	Psoriasis may impair male fertility possibly due to systemic inflammation
Heppt F (37)	2017	27 male patients receiving either TNF-a inhibitors or fumaric acid esters	85.2% of patients had at least one sperm abnormality. 48.1% showed parameter of GTI	Treatment with TNF-a inhibitors or fumaric acid esters revealed no effect on sperm quality
Grunnet E (38)	1977	10 psoriatic males treated with topical corticosteroids and 10 psoriatic patients under MTX therapy	Reduced sperm qualities possibly induced by the psoriatic lesions in the genital tract	MTX therapy seems safe
Hui Liu (39)	2017	31 psoriatic patients under acitretin treatment and	Normal sperm motility and appearance during and after	Different doses of acitretin did not affect significantly semen quality

		14 healthy controls	withdrawing the regimen	
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Note: SHBG=sex hormone -binding globulin, **TNF**= tumor necrosis factor,**GTI**=genital tract infection, **MTX**= methotrexate

Sarcoidosis

Three publications were selected regarding the association of sarcoidosis with male infertility. Svetec in 1998 studied the case of a 36-year-old male with epididymal sarcoidosis and came to the conclusion that epididymal sarcoidosis may lead to intermittent azoospermia (40). Another case report of a 23-year-old with bilateral testicular sarcoidosis demonstrated severely impaired spermatogenesis, through semen analysis, that was improved after corticosteroid treatment (41). Subsequent data of Kovac’s publication confirmed the role of prednisone in the restoration of fertility comparing the semen analysis results of a male patient with genitourinary sarcoidosis and azoospermia before and after the regimen(42).

Table 9- Sarcoidosis and male fertility

Author	Year	Study population	Conclusion
Svetec (40)	1998	36-year-old male with secondary infertility and epididymal sarcoidosis	Epididymal sarcoidosis can be associated with intermittent azoospermia
Takiguchi (41)	2008	23-year-old Japanese man with asymptomatic bilateral testicular lesions	Testicular sarcoidosis may cause male infertility
Kovac (42)	2012	37-year-old male who initially presented for azoospermia and secondary infertility	Significant improvements noted after prednisone treatments

DISCUSSION

Systemic lupus erythematosus affects about 5 million people worldwide and is mostly developed between the ages of 15 and 44. Systemic lupus erythematosus strikes mostly

women; however, impaired fertility has been revealed through many papers for both sexes. All eight papers reviewed in this publication reported hormonal, testicular or seminal abnormalities in male SLE patients. Five papers indicated IV CYC as the major factor that led to these abnormalities (6,7,8,9,12). Moreover, erectile dysfunction, elevated levels of FSH and LH (10,11,13), as well as Sertoli cells dysfunction (11) have been observed and correlated to male infertility.

Behcet's disease is an inflammatory disorder that affects multiple parts of the human body. Painful genital ulcerations can be developed and have been accused of the semen abnormalities reported in several BD patients. Azoospermia and oligospermia are also present in these patients (14,15). IV CYC seems to have a major impact on these findings (14) whereas colchicine use does not seem to have an adverse effect on sperm production (16).

On the other hand, colchicine may impair reproductive function in male patients with Gout, as some patients seem to be unusually sensitive to its toxic effect (17). However, Gout which is characterized by elevated levels of uric acid in blood affects mostly patients over 50 years old who have already procreated.

Dermatomyositis, whose main symptoms include several signs of skin rash as well as muscle weakness, may lead to several semen abnormalities (18). Nevertheless, more studies are needed in order to identify this connection.

Coeliac disease is a long-term autoimmune disorder that primarily affects the small intestine and is caused by a reaction to gluten. Pregnancy complications, such as miscarriage or preterm birth have been reported in female patients. One study, reviewed in this paper, revealed an increase of FSH and LH levels in untreated CD male patients probably caused by an impairment of the pituitary regulation (19).

Rheumatoid arthritis affects between 0.5% and 1% of adults in the developed world. RA patients under MTX treatment must be counselled on its adverse effects on fertility. One of the papers indicated that sulphasalazine (23) may impair male fertility and another one that antisperm antibodies (25), which can interfere with sperm motility and transport through the female reproductive tract, may be elevated by RA's activity.

Ankylosing spondylitis, which is commoner in men and affects between 0,1 and 1,8 of world population is nowadays treated mostly with TNF-a blockers. Two of the reviewed papers proved that their use has no effect on male fertility. On the other hand, the presence of varicocele in many AS patients as well as the sperm form abnormalities, possibly caused by the disease, could lead to the observed impairment of fertility.

Inflammatory bowel disease is a group of inflammatory conditions of the colon and the small intestine whose principal types are Crohn's disease and ulcerative colitis. The five studies that were reviewed showed the impact of the medical therapies used for IBD such as mesalazine, infliximab and methotrexate may affect fertility by impairing the sperm motility and total sperm count. Anti-TNF treatment was once more described as the safest therapy.

About 4% of the global population suffer from psoriasis. This disease affects both sexes equally probably by causing inflammation of the genital tract. Sperm abnormalities (37), decreased sperm motility as well as lower testosterone and SHBG levels (36) are frequent in male psoriatic patients. However, a more extensive evaluation of these parameters is needed in order to identify the correlation with the psoriatic manifestations.

Sarcoidosis, frequently leads to amenorrhea and galactorrhoea in women as a result of prolactin levels increase. In male patients, epididymis and testicles may be affected leading to male infertility. Testicular involvement has been reported in about 5% of patients through biopsy and its impact on fertility is still under research (40,41).

ABBREVIATIONS

AS= Ankylosing spondylitis

BD= Behcet disease

CD= Coeliac disease

DM= Dermatomyositis

IBD= Inflammatory bowel disease

RA= Rheumatoid arthritis

SLE= Systemic lupus erythematosus

IV= Intra venus

FSH= Follicle-stimulating hormone

LH= Luteinizing hormone

u/s=Ultrasound

LHRH= Luteinizing hormone-releasing hormone

TNF= Tumor necrosis factor

DNA= Deoxyribonucleic acid

CYC= Cyclophosphamide

SHBG= Sex hormone -binding globulin

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