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# Autoimmune Diseases and Male Fertility: A Systematic Review

**Evangelos Iliopoulos***

## 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.

**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.

**Conclusion:** Thirty-nine articles were finally included regarding the following diseases: Dermatomyositis, Systemic Lupus Erythematosus, Behcet's disease, Gout, Celiac disease, Rheumatoid arthritis, Ankylosing spondylitis, Inflammatory bowel disease, Psoriasis, Sarcoidosis 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-TNF treatment in ankylosing spondylitis does not affect the fertility potential. Antisperm antibodies and sulphasalazine treatment 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. Fertility impairment is common in autoimmune diseases. Henceforth, more studies are needed to identify the relationship between fertility and immunity.

### Keywords

Autoimmune diseases; Male fertility; Sperm abnormalities; Semen quality; Fertility impairment

### 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 Globuin

***Corresponding author:** Evangelos Iliopoulos, Department of Obstetrics and Gynecology, Elena Venizelou Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Timfristou 84, Chalandri, Greece, Tel: 00306975779682; E-mail: aggelos.iliop@gmail om

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## 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 regimens 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 the 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 a 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). Two papers 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 [4]. 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

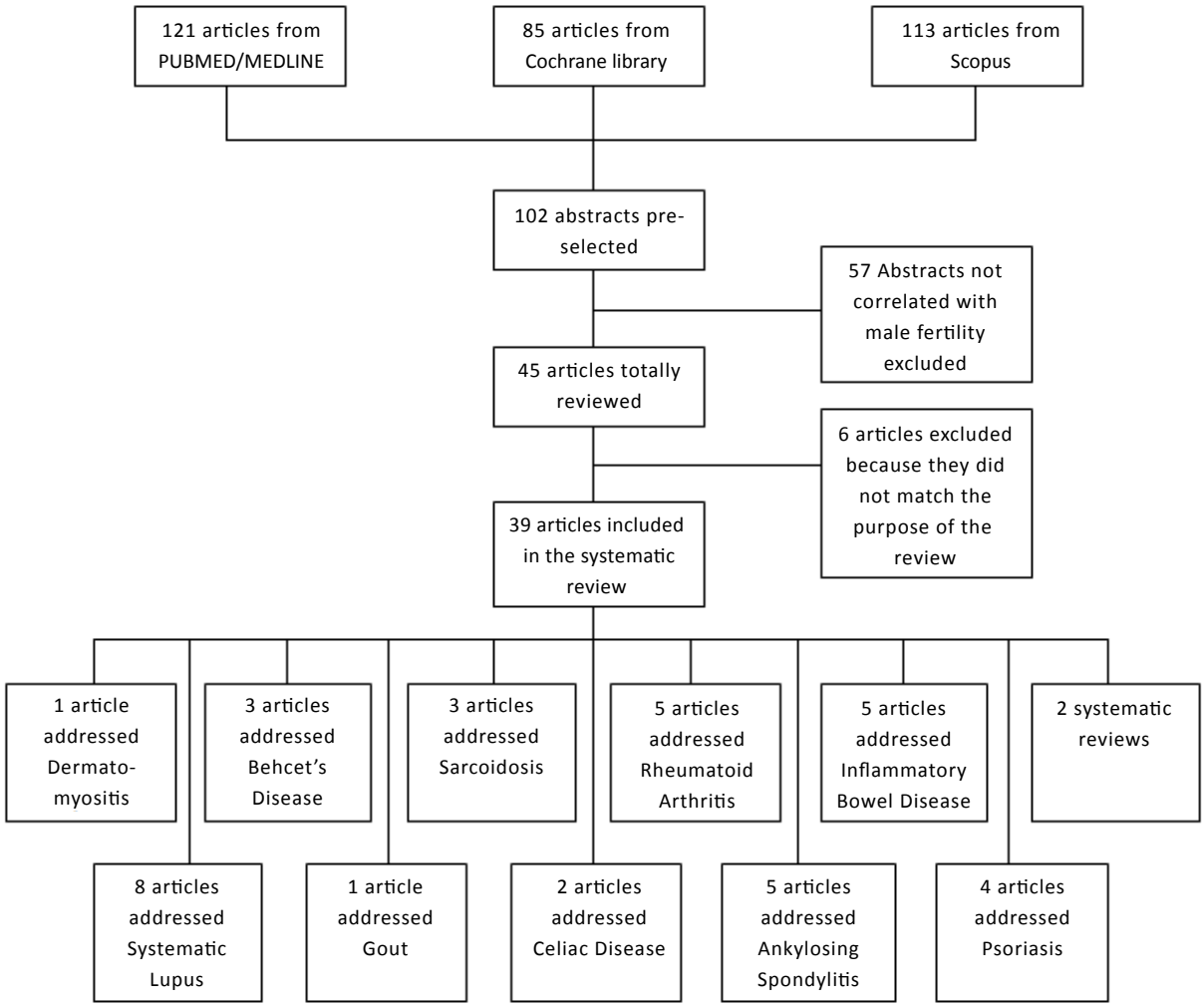


**Figure 1:** Search and selection.

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 [8].

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 [9].

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 [10]. 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 [11].

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 [12].

## 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 [13]. 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 parameter 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 color flow, Doppler sonography oligonecrospermia, and arterial insufficiency were revealed in approximately one-third of the patients [14].

On the other hand, Haimov-Kochman doubts the link between colchicine and male infertility implying that sperm pathology is caused by the underlying disease (Table 2) [15].

## 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 [16]. Results revealed that 11% of the spermatozoa displayed 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 [17]. 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 based on 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. Also, one of the patients who was treated with a high dose of intravenous cyclophosphamide had oligoasthenoterato zoospermia which was normalized five years after the treatment's interruption (Table 3).

## 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 celiac disease with 19 men with Crohn's disease of similar age [18]. 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 normal fertility in men with celiac disease as the overall fertility hazard ratio in men was 1.01 (Table 4) [19].

## Rheumatoid Arthritis

Five publications selected focused on the aspects of male

**Table 1:** Systemic lupus erythematosus and male infertility.

| Author | Year | Study population | Results | Conclusion |
|---|---|---|---|---|
| Rabelo-Junior CN | 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 | 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 | 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 | 2017 | SLE patients(review from several papers) | Drugs used for SLE, especiallyIV 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 | 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 |
| Suehiro | 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 | 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 | 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 |

SLE: Systemic Lupus Erythematosus; APS: Antiphospholipid Syndrome; IV: Intra Venus; CYC: Cyclophosphamide; FSH: Follicle-Stimulating Hormone; LH: Luteinizing Hormone; u/s: Ultrasound

**Table 2:** Behcet's disease and male infertility.

| Author | Year | Study population | Results | Conclusion |
|---|---|---|---|---|
| Fukutani | 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 | 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 | 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 |

BD: Behcet's Disease; CYC: Cyclophosphamide; FSH: Follicle-Stimulating Hormone; FMF: Familial Mediterranean Fever

fertility in rheumatoid arthritis. A study of 2017 suggested that patients treated with methotrexate for rheumatoid arthritis must be counseled of discontinuation before conception as well as of sperm cryopreservation [20]. 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 [21].

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 [22]. 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 [23] 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 (Table 5) [24].

## Ankylosing Spondylitis

Five publications assessed male fertility on patients with ankylosing 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 [25].

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 [26]. 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 [27].

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 [28]. 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 (Table 6) [29].

## Inflammatory Bowel Disease

Five publications regarding the association between inflammatory bowel disease and male infertility were selected. A study of 2017 revealed better sperm concentration and motility in men treated with anti-tumor necrosis factors than those who were on another regimen [30]. 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 [31].

**Table 3:** Gout, dermatomyositis and male fertility.

| Author | Year | Study population | Results | Conclusion |
|---|---|---|---|---|
| Kastrop P. | 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 | 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 |
| FISH: Fluorescence *in situ* Hybridization; IV: Intra Venus; CYC: Cyclophosphamide; DM: Deratomyositis | | | | |

**Table 4:** Coeliac disease male fertility.

| Author | Year | Study population | Results | Conclusion |
|---|---|---|---|---|
| Farthing MJ | 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 | 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 |
| CD: Coeliac Disease; FSH: Follicle-Stimulating Hormone; LH: Luteinizing Hormone | | | | |

**Table 5:** Rheumatoid arthritis and male fertility.

| Author | Year | Study population | Results | Conclusion |
|---|---|---|---|---|
| Guttierez JC | 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 | 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 | 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 | 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 | 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 |
| RA: Rheumatoid Arthritis; MTX: Methotrexate; FSH: Follicle-Stimulating Hormone; LH: Luteinizing Hormone | | | | |

crossover-crossback prospective study brought attention to possible side-effects of exposure to high dibutil-phthalate mesalazine as the men studied had decreased sperm motility and sperm count even after crossback to non dibutil-phtalate mesalazine [32]. 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 (Table 7) [34].

## 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 an andrological examination. Lower testosterone and sex hormone-binding globulin levels in addition to inflammation of the accessory glands were observed in psoriatic patients [35]. 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 [36]. 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 [37]. 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 (Table 8) [38].

## 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 concluded that epididymal sarcoidosis may lead to intermittent azoospermia [39]. 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 [40]. 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 (Table 9) [41].

**Table 6:** Ankylosing spondylitis and male fertility.

| Author | Year | Study population | Results | Conclusion |
|---|---|---|---|---|
| Chazimeletiou | 2018 | One patient | Headneck and tale abnormalities/ immature sperm forms | AS may affect male fertility |
| Micou | 2014 | 23 AS patients and 42 controls | No statistically significant difference in sperm quality | Sperm quality was not affected by TNF-a therapy |
| Almeida | 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 | 2009 | 4 AS patients treated with Infliximab | All patients had at least one child | Infliximab is not associate with infertility issues |
| Nukumizu | 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 |

AS: Ankylosing Spondylitis; TNF-a: Tumor Necrosis Factor-a

**Table 7:** Inflammatory bowel disease and male fertility.

| Author | Year | Study population | Results | Conclusion |
|---|---|---|---|---|
| Valer P | 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 | 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 | 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 | 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 | 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 |

IBD: Inflammatory Bowel Disease; TNF: Tumor Necrosis Factor; MTX: Methotrexate; DNA: Deoxyribonucleic Acid; DBP: Dibutyl Phthalate

**Table 8:** Psoriasis and male fertility.

| Author | Year | Study population | Results | Conclusion |
|---|---|---|---|---|
| Caldarola G | 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 | 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 | 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 | 2017 | 31 psoriatic patients under acitretin treatment and 14 healthy controls | Normal sperm motility and appearance during and after withdrawing the regimen | Different doses of acitretin did not affect significantly semen quality |
| SHBG: Sex Hormone-Binding Globulin; TNF: Tumor Necrosis Factor; GTI: Genital Tract Infection; MTX: Methotrexate | | | | |

**Table 9:** Sarcoidosis and male fertility.

| Author | Year | Study population | Results | Conclusion |
|---|---|---|---|---|
| Svetec | 1998 | 50 male psoriatic patients and 50 healthy age-matched controls | 36-year-old male with secondary infertility and epididymal sarcoidosis | Epididymal sarcoidosis can be associated with intermittent azoospermia |
| Takiguchi | 2008 | 27 male patients receiving either TNF-a inhibitors or fumaric acid esters | 23-year-old Japanese man with asymptomatic bilateral testicular lesions | Testicular sarcoidosis may cause male infertility |
| Kovac | 2012 | 10 psoriatic males treated with topical corticosteroids and 10 psoriatic patients under MTX therapy | 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 [4,6-8,11]. Moreover, erectile dysfunction, elevated levels of FSH and LH [9,10,12], as well as Sertoli cells dysfunction [10] 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 [13,14]. IV CYC seems to have a major impact on these findings [13] whereas colchicine use does not seem to have an adverse effect on sperm production [15].

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 [16]. 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 [17]. Nevertheless, more studies are needed 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 [18].

Rheumatoid arthritis affects between 0.5% and 1% of adults in the developed world. RA patients under MTX treatment must be counseled on its adverse effects on fertility. One of the papers indicated that sulphasalazine [22] may impair male fertility and another one that antisperm antibodies [24], 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 the world population is nowadays treated mostly with TNF-a blockers. Two of the reviewed papers proved that their use does not affect 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 sperm motility and total sperm count. Anti-TNF treatment was once more described as the safest therapy.

About 4% of the global population suffers from psoriasis. This disease affects both sexes equally probably by causing inflammation of the genital tract. Sperm abnormalities [36], decreased sperm motility, as well as lower testosterone and SHBG levels [37], are frequent in male psoriatic patients. However, a more extensive evaluation of these parameters is needed 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 [39,40,42,43].

## Conclusion

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

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