

# Influence of psoriasis and inflammatory bowel diseases on reproduction and fertility

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## Abstract

Autoimmune diseases (AD) are a wide group of diseases the essence of which is the inflammatory process inside the body. Psoriasis, a chronic inflammatory skin disease with a complex pathogenesis consisting of a genetic component, immune dysfunction, and environmental factors, affects 2–4% of the general population. Inflammatory bowel diseases (IBD) have emerged as global diseases. Both ulcerative colitis (UC) and Crohns disease (CD) affect over two million individuals in North America, three point two million in Europe, and millions more worldwide. An increasing number of people at reproductive age have difficulties achieving pregnancy. Therefore, infertility has been considered by the World Health Organization as a social disease.

This study is to aimed the discuss the influence of immune diseases on human fertility. We focused mainly on recently published articles.

Summing up, the autoimmune diseases affect human fertility by limiting and disrupting reproductive capacity. The coexistence of autoimmune diseases in people of reproductive age is not a contraindication to reproduction. One of the factors that has a significant impact on fertility is the use of immunomodulating drugs, including methotrexate. Research into the effects of biological drugs on the reproductive capacity of people with autoimmune diseases should be intensified. More research is needed to fully understand the pathogenesis of reproductive disorders in people with autoimmune diseases.

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fertility, psoriatic disease, inflammatory bowel disease, reproductive health

## Introduction

Autoimmune diseases (AD) are a wide group of diseases the essence of which is the inflammatory process inside the body. Currently, it is estimated that autoimmune diseases affect approximately 3-5% of the population. Most of them are hypothyroidism and type 1 diabetes mellitus [1]. Diseases such as psoriasis and inflammatory bowel disease (IBS) are not uncommon. In general population occur with frequency of 2-4% in psoriasis and 3% in IBS [2,3].

Significant progress has been made in the diagnosis and classification of autoimmune diseases over the last few years [1]. Contemporary theories suggest that the development of autoimmune disease is related to genetic predisposition and environmental factors that trigger immune pathways that ultimately lead to tissue destruction. Despite extensive research, there are no genetic tools that can be used clinically to predict the risk of autoimmune disease.

Reproductive problems are common in people with autoimmune diseases [4]. They are diseases from potentially distant fields of medicine such as reproductive medicine and immunology. However, there are many similarities and interrelationships between them that have not been thoroughly investigated.

According to World Health Organization fertility is the term that describes the likelihood of a couple getting pregnant during their menstrual cycle. The reproductive age is defined as the period between puberty and the menopause. With age, human reproductive abilities decrease, this applies to both women and men. The WHO has defined the word infertility as the inability to get pregnant after 12 months or more, having had regular unprotected intercourse. Infertility is defined as a separate disease entity. It has been proven that people with autoimmune diseases have a lower reproductive potential and are more often affected by the problem of infertility. There are many factors that influence and modulate fertility in people suffering from autoimmune diseases [4,5,6].

It has been proven that autoimmune diseases affect women more often. Women with autoimmune diseases, optimizing reproductive health requires continuous and multidisciplinary care that begins well before the desire to become pregnant is expressed [1].

Family planning is essential so that pregnancy can be planned when the disease is stable and that medications can be adjusted accordingly. Autoimmune diseases in women usually appear in young and middle adulthood. The incidence rates of women compared with men vary after adolescence. While the explanation for the predominance of autoimmune diseases among women remains elusive, gonadotropic hormones and reproductive transformations are believed to modulate the risk of autoimmune diseases. It is also believed that the microchimerism of maternal fetal cells, which arises as a result of transplacental exchange and may persist for decades after pregnancy, may play a role in maternal autoimmunity [7].

## Objective and Review Questions

The aim of this study is to discuss the influence of immune diseases on human fertility. This work is a compilation of assessments of the effects of direct disease activity, autoimmune factors and drugs used. The literature review consisted of searching the Medline, PubMed and Google Scholar databases. The following words and phrases were used during the search: autoimmune diseases, infertility, psoriasis, inflammatory bowel disease, both in English and Polish. We focused mainly on recently published articles. Despite a fairly good understanding of infertility and autoimmune diseases, there remains a little-known problem of these diseases as factors that affect one patient together. Moreover, there are still few reports in the literature regarding the influence of psoriasis and IBS on human fertility.

## Results and discussion

Human fertility is an extremely broad topic in the field of public and reproductive health. Women and men are susceptible for most of their lives to environmental factors that can modulate reproduction. They can have a negative effect at all stages leading to the development of the offspring, starting from the production and function of gonads, through the process

of gamete formation and maturation, fertilization to ending with the embryo and fetus maturation. Mere exposure to potentially harmful agents is not a sure indicator of reproductive failure. For the occurrence of possible infertility, i.e. the appearance of a negative influence of these factors, a specific duration of action, potency, individual predisposition of a given person and the presence of comorbidities are necessary. The occurrence of infertility may be temporary, when it resolves spontaneously or after infertility treatment, or permanent, in which case the term infertility may be used.

One of the most common diseases with a complex etiology which includes an autoimmune component is psoriasis. Psoriasis affects about 2% of the population. It can be assumed that the generalized inflammation associated with psoriasis may affect reproductive functions by affecting the environment of the ovum maturation [5]. According to scientists, this has a negative effect on the reproductive capacity of women [6,8].

In a publication published in 2021 by our team was shown that excess body fat adversely affects the reproductive function of women, especially in the presence of psoriasis. Moreover, we have shown that psoriasis burden in combination with excess body weight influences the risk of intrauterine growth restriction. The study included 140 women (110 healthy and 30 with psoriasis). In the group of healthy women, BMI negatively correlated with total recovery, total oocyte score, rate of blastocyst formation (BFR), and the amount and quality of blastocysts. The relationships were similar in psoriasis. In the group of healthy patients, BMI negatively correlated with the gestational age at delivery and the APGAR score [5].

Women with moderate to severe psoriasis in Spain showed a reduction of more than 50% in age-adjusted fertility rates compared to the general population, which is comparable to the effectiveness of the ICSI procedure in this study among 30 women with mild plaque psoriasis. This fact can be explained in a study by Tuğrul Ayanoğlu B. et al. [9], who observed a lower ovarian reserve in patients with psoriasis compared to their healthy peers.

It should also be mentioned that Patients with autoimmune diseases, such as psoriasis or IBS, are

usually treated with systemic immunomodulating and teratogenic drugs, such as methotrexate, cyclosporine or retinoids, which may significantly affect conception and the course of pregnancy [4,5].

Several studies have found reversible changes in semen parameters in patients treated with methotrexate. In the case reported by Sussman et al. a young man with severe psoriasis was treated intermittently with MTX at a dose of 30 mg/week. Multiple semen samples were collected and sperm concentration and cellular morphology were analyzed [10]. Within 3 weeks of treatment, the patient's sperm concentration decreased and morphological examination showed a reduction in the percentage of oval forms (i.e. mature sperm) and an increase in the percentage of immature germ cells and early sperm. Spermatogonia, not normally found in the seminal fluid, occurred 2–3 weeks after MTX treatment. After discontinuation of MTX therapy, a rapid recovery of sperm count and normalization of sperm morphology (no spermatocytes and spermatogonia were detected) were observed in the patient, which suggests a potential reversibility of oligospermia [11]. Interestingly, the patient developed oligospermia while his psoriasis clinically improved, also indicating a lack of evidence and clinical knowledge about the effects of disease severity alone on fertility. Similar results were obtained in the case report of a 32-year-old man treated with MTX for bilateral seminoma. The evaluation showed a significant decrease in sperm count and motility, and an increase in abnormal sperm morphology. Three months after stopping treatment, sperm parameters returned to pre-treatment levels and the patient sired two healthy descendants. This pattern of results was seen after two treatment cycles and treatment discontinuation.

It has been proven that during treatment with MTX, sperm counts decrease and become immobilized within 4 to 20 weeks [11]. Since spermatogenesis takes 74 days to complete, it is difficult to explain the sharp drop in sperm count after starting MTX. To explain this decrease, MTX must interfere with some late events in the spermatogenesis cycle, namely spermiogenesis (conversion of spermatids to mature sperm) [12]. The exact mechanism of this process has not been yet elucidated, but a study in mice treated with MTX suggested that inhibition of late

sperm and earlier germ cell precursors might be a viable pathway to induce these results [13]. Many studies on MTX, including the above-mentioned ones, are confused by combining use with other treatment regimens, making it difficult to establish the true effect of MTX on male fertility [14].

In an excellent review, which was published in December 2021 under the title: "Impact of Psoriasis and Hidradenitis Suppurativa in Pregnancy, a Systematic Review", the authors emphasized the negative impact of inflammatory skin diseases not only on fertility itself as the possibility of giving birth to a child, but also on the willingness to having a child and the impact of pregnancy on the development and stability of the disease. This work deserves increased attention due to the enormous amount of scientific evidence that has been taken into account in collecting the data. The above-mentioned review also drew attention to an extremely important, but underestimated aspect, which is the change of the therapy of the underlying disease that has been used so far. Nowadays, the most effective method of treating autoimmune diseases, especially in the most difficult cases, is biological treatment. Biological treatment is relatively modern and usually quite expensive therapy, which is associated with side effects, but it is the last resort for success in fighting the disease. In Europe, the period of pregnancy and the time of possible preparations for pregnancy for people suffering from autoimmune diseases is often associated with a change in the method of treatment, including biological treatment. This is due to ambiguous recommendations or guidelines of societies scientific research or insufficient knowledge of doctors treating sick people.

The authors, Ferrer-Alcalá et al. emphasize that, on the basis of the available scientific evidence, biological therapy during pregnancy is safe, and pregnancies conducted with biological therapy have a great chance of reaching the term of delivery without complications, and that children born of such pregnancies are healthy [12]. The treatment tested in all articles included in the above-mentioned review are biological drugs [15]. The presented studies show that the burden of psoriasis has a negative impact on human reproductive functions from the stage of gametogenesis, through conception,

early embryonic stage and pregnancy, as well as the condition of the newborn.

Another group of autoimmune diseases that occur quite frequently are inflammatory bowel diseases (IBD). Infertility and IBD are diseases from potentially remote areas of medicine, such as reproductive medicine and gastroenterology. However, there are many similarities and interrelationships between them that have not been thoroughly investigated. IBD is a group of unexplained diseases whose main representatives are Crohn's disease and ulcerative colitis(UC). Their range is worldwide, they affect millions of patients all over the world, their course is long, usually lifelong, and their incidence increases especially in developed countries [3,5]. The main symptoms relate to the digestive system, especially the lower gastrointestinal tract, but clinical signs may affect the entire body. The treatment uses drugs that have a documented effect on a man's reproductive ability, and are even prohibited when trying to conceive a child. The therapy usually begins at the time of diagnosis, which is usually between the ages of 20 and 30 – in the period of the greatest fertility of a human being [16].

It has been shown in UC patients that long-term administration of 5-ASA may cause abnormal sperm parameters, including impaired sperm motility, increased abnormal sperm morphology, and decreased sperm concentration [9,16–18]. MTX is often used as a second-line immunomodulatory agent in IBD patients who are resistant or intolerant to thiopurines and are known to induce MTX oligospermia due to its antifolate activity, with consequent inhibition of DNA synthesis and cell proliferation [11,19]. A recent study by Ley et al. Showed a significantly reduced sperm integrity secondary to oxidative stress compared to men of the same age in IBD patients who received MTX for > 3 months [13].

The role of other drugs, including azathioprine (AZA) and 6-mercaptopurine (6MP), as well as steroids, has not been yet clearly established. However, no studies have shown any significant adverse effects on male fertility or the course of pregnancy [7,20,21]. Similarly, single reports from clinical trials with biological drugs indicate that, at least in the majority of those prescribed, they did not cause

adverse outcomes in pregnancy and male infertility [12, 20–24]. For example, there is evidence to suggest that infertility is more prevalent in patients with IBD than the general population owing to a mechanism outside of exposure to a particular medication, but rather in the presence of antibodies [4,25]. Interestingly, Weber-Schoendorfer et al. found that the rate of elective termination of pregnancies was increased (although not significant) in men treated with MTX compared to the control group. The reason for the termination of pregnancy has not been established, but it could have been caused by the fear of the transmission of paternal disease or the uncertain negative influence of drugs on fertility [10,26].

It has been proven that patients with systemic autoimmune diseases have fewer children than in the general population. Some of these women have no children at all, others report a longer time to get pregnant, which results in less amount family size than expected [5]. Certainly, the number of children in this population may also be associated with an often organ-related autoimmune disease. However, there are many other factors to consider. The disease itself and the related musculoskeletal limitations may impair sexual function and psychologically affect a woman's desire [27]. Moreover, in systemic autoimmune diseases, also abnormalities related to the clinical picture of the body, associated low self-esteem and depression may affect the personal and sexual relations of these women [28,29].

## Conclusions

Autoimmune diseases affect human fertility by limiting and disrupting reproductive capacity. The coexistence of autoimmune diseases in people of reproductive age is not a contraindication to reproduction. One of the factors that has a significant impact on fertility is the use of immunomodulating drugs, including methotrexate. Research into the effects of biological drugs on the reproductive capacity of people with autoimmune diseases should be intensified. More research is needed to fully understand the pathogenesis of reproductive disorders in people with autoimmune diseases.

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