Psoriasis and inflammatory bowel diseases as a health problem for people of reproductive age

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Abstract

Psoriasis and IBS are autoimmune diseases that usually appear at an early age for the first time and may sometimes coexist. If they coexist, the patient requires multidisciplinary care, especially in the case of reproductive plans, due to the proven increased risk of infertility. The aim of this study was to discuss psoriasis and inflammatory bowel diseases as diseases that often occur in young people and how it may affect human reproduction. The literature review consisted of searching the Medline, PubMed and Google Scholar databases. The following words and phrases were used during the search: infertility, psoriasis, IBD. This paper presents treatment options for patients with psoriasis and / or IBS who are planning pregnancy and are pregnant. The possibility of treatment with general drugs was emphasized, and biological drugs were taken into account. Most systemic drugs are contraindicated when trying for a pregnant, during pregnancy and during breastfeeding. Some biological medications appear to be a safe alternative for women with psoriasis and / or IBS flare-ups during pregnancy or breastfeeding. It would be advisable to establish an algorithm for the treatment of people with psoriasis, IBS, who have problems with infertility. The cooperation of gynecologists, dermatologists and gastroenerologists is necessary.

Key words:

psoriasis, infertility, IBS

Introduction

In the case of the coexistence of an autoimmune disease, a person of reproductive age requires a multidisciplinary therapeutic and therapeutic approach. With the coexistence of several autoimmune inflammatory diseases, especially in young people of reproductive age, the cooperation of the gynecologist with doctors of other specialties is crucial. Psoriasis and inflammatory bowel diseases are a group of autoimmune diseases that can coexist. In the case of young people, the cooperation of gynecologists, gastroenterologists and dermatologists is important.

Psoriasis is a multi-gene autoimmune inflammatory disease that affects approximately 1-3% of the population [1]. Chronic inflammation plays a major role in its pathogenesis, which leads to the uncontrolled proliferation of keratinocytes, which leads to the growth of the epidermis. Responsible for this are macrophages, T lymphocytes and neutrophils. T cells play a key role in the etiology of psoriasis. CD4 + and CD8 + cells are found in the epidermis and in the upper layer of the dermis, but CD4 + is the dominant one. T cells also produce other mediators such as: INF-gamma, IL-2, IL-17, TNFalpha. An important aspect in the pathogenesis of psoriasis is also neovascularization [2]. One of the most important cells involved in the pathogenesis of the initial stages of psoriasis are dendritic cells. Their role has not been fully understood. One proposed mechanism involves the recognition of antimicrobial peptides (AMP), which are secreted by keratinocytes in response to injury and are overexpressed in the skin of patients with psoriasis. Among the most studied AMPs associated with psoriasis are the proteins LL37, β-defensin, and S100 [3].

A lot of has been done to date on the relationship between psoriasis and HLA. The inheritance of psoriasis is multi-gene, non-autosomal dominant and non-autosomal recessive. Presumably, multiple alleles encoded by several genes are required to reveal the disease.

The analysis of HLA compounds made it possible to distinguish two types of psoriasis. Type I applies to patients under 40 years of age. This type is combined with HLA: Cw6, B13, Bw57 and a small percentage with Cw2. Type I is prone to severe disease and inheritance. Type II, on the other hand, is characterized by the onset after the age of 40. There is no family tendency to perform. Type I is more common and affects up to two thirds of the population [4].

Inflammatory bowel disease (IBD) is a group of diseases that include Crohn's disease and ulcerative colitis. It is a group of diseases associated with chronic inflammation in the digestive tract. The most common symptoms of IBD are diarrhea, abdominal pain, weight loss [5]. The development of IBD occurs as a result of an excessive immune response of the system to the activity of intestinal bacteria, especially in genetically predisposed persons. The reaction against bacteria is conditioned, among others, by mutations in the NOD2, ATG16L1 and IRGM genes responsible for innate immunity and autophagy. NOD2 mutations are also associated with impaired production of defensins in the ileum [6]. Innate immune cells such as monocytes, neutrophils, and natural killer (NK) cells cannot kill the bacteria which function as antigens and stimulate intestinal mucosal cells to cause immune responses [7]. The two main types of IBD represent distinct forms of gut inflammation: CD is associated with Th1 response whereas UC with Th2 response. Th17 cells are involved in the gut inflammatory response in IBD [8].

Both diseases can affect both adolescents and adults and affect men and women equally [9].

The peak age of diagnosis of inflammatory bowel disease (IBD) is years in the human reproductive period, therefore treatment of inflammatory bowel disease during pregnancy is a common phenomenon. Maintaining disease remission is critical to optimizing pregnancy outcomes, and the potential maternal or fetal toxicity of drugs should be weighed against the risk of untreated IBD [10].

Infertility has been defined by the WHO as a disease. Its range is huge and reaches even 15% of the population. Reproductive failures affect people trying to conceive a child, i.e. people of reproductive age. According to WHO, infertility is defined as the lack of a child after 12 months of regular intercourse (3-4 times a week) without the use of contraception [11]. Psoriasis and inflammatory diseases are

autoimmune diseases that affect young people much more often, often in their reproductive years.

Objective and Review Questions

The aim of this study was to discuss psoriasis and inflammatory bowel diseases as diseases that often occur in young people and may affect human reproduction. The literature review consisted of searching the Medline, PubMed and Google Scholar databases. The following words and phrases were used during the search: infertility, psoriasis, IBD. We focused mainly on recently published articles. Despite a fairly good understanding of infertility, BD and psoriasis there remains a little-known problem of these diseases as factors that affect one patient together.

Results and discussion

Both psoriasis and IBD are disease entities that usually appear at a young age, very often during the reproductive period. Based on worldwide systematic review of the epidemiology of psoriasis the estimated prevalence of this disease in adults ranged from 0.51% to 11.43%, and in children from 0% to 1.37% [12]. The most common cases of IBD are reported between the ages of 15–35. The annual incidence of ulcerative colitis varies from 0–19.2 per 100,000 in North America and 0.6–24.3 per 100,000 in Europe, corresponding to a prevalence of 37.5–248.6 per 100,000 and 4.9–505 per 100,000, respectively. The incidence of Crohn's disease is similar (0–20.2 per 100,000 in North America; 0.3–12.7 per 100,000 in Europe) [13].

UC is estimated to affect 2.6 million in Europe and 1.2 million people in North America [14]. About 25% of these patients are diagnosed before the age of 18. The disease often begins in adolescence, and approximately 25% of IBD patients are under 20 years of age [15].

The mainstay of therapy for patients with IBD or psoriasis are systemic drugs, often immunosuppressants or biological drugs.

Patients are very often concerned about side effects of drugs, they are often exacerbated during pregnancy due to additional concern about toxicity to the fetus [16]. Patients' misconceptions and unjustified fears of drug teratogenicity contribute to drug failure during pregnancy and breastfeeding [17-21]. Lack of complience between the physician and the patient predisposes to active IBD or psoriasis, which is associated with poorer pregnancy outcomes, including an increased rate of premature births, low birth weight (LBW), spontaneous abortion and delivery by caesarean section [22]. Women and men of childbearing age should see their doctor prior to conception to provide accurate information on fertility, pregnancy, and drug safety, and to optimize pregnancy outcomes. The balance between minimizing both drug toxicity and active disease should be explained to patients, as well as the overall population risk of adverse events such as spontaneous abortion (approximately 10-30%) and birth defects (3%) [23].

It has been shown that women with psoriasis were more likely to use assisted reproductive technology-based treatments, which indicates that these women or their partner have a problem with becoming pregnant. Johansen et al. Conducted a case-control study which found that women with psoriasis had an increased risk of ectopic pregnancy. The absolute risk of ectopic pregnancy was 2.48% higher in women with moderate to severe psoriasis compared to healthy women. Perhaps this is due to the fact that women with more severe psoriasis tend to have tubal implantation, which may be related to a malfunctioning immune system in these patients. For the implantation of the embryo to proceed properly, it is necessary to develop an immunological tolerance so that the body can accept the foreign embryo. Then there is an advantage of regulatory T lymphocytes over Th17, the type of immune response dominates 2. It should be noted that in patients suffering from autoimmune diseases, Th17 lymphocytes may prevail and the activity of regulatory T lymphocytes may decrease. This hypothesis is reinforced by the common immune pathway of psoriasis with IBD, which is also associated with an increased risk of ectopic pregnancy [24].

About 15% of women experience a worsening of psoriasis during pregnancy. In the case of severe

psoriasis, it is necessary to use general medications. In the treatment of psoriasis, methotrexate, acitretin and cyclosporine are used [25].

Cyclosporin A is a drug that is used both in the treatment of severe psoriasis and in the salvage treatment of steroid-refractory acute severe ulcerative colitis (UC) as an alternative to anti-TNF drugs. Ciclosporin can cross the placenta, reaching fetal levels of 10-50% of maternal levels [26].

Ciclosporin is not teratogenic, however it may increase the risk of preterm labor. Also note that CyA capsules contain ethanol. Due to the dissolution of CyA in fats, this drug passes into the milk of nursing mothers, therefore CyA should not be used during breastfeeding, and if the lactating mother is taking CyA, she should be advised to switch to artificial feeding. The use of ciclosporin during pregnancy is associated with an increased risk of low birth weight and preterm labor. In addition, patients with concomitant cardiovascular diseases are at greater risk of developing hypertension [27].

Acitretin, like other retinoids, is a highly teratogenic drug. For this reason, it must not be given to pregnant women, and effective methods of contraception must be used by all women during reproductive age taking this medicine. Since acitretin metabolites are stored in adipose tissue, pregnancy is strictly contraindicated for 3 years after the end of therapy. Men can use acitretin without restrictions on conceiving a child [27].

MTX is often used as a second-line immunomodulatory agent in IBD patients and in those who are resistant or intolerant to thiopury [28]. In addition, methotrexate is used in the treatment of severe psoriasis. MTX has been shown to induce oligospermia due to its antifolate activity, which consequently inhibits DNA synthesis and cell proliferation [29]. 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 more than 3 months. [30]. A recent prospective cohort study documented a significantly higher rate of spontaneous abortion (42.5%) and major birth defects (6.6%) in women exposed to methotrexate after conception compared to women exposed only before conception (14.4% and 3, respectively). 5%), while the rates in the latter cohort are comparable to those of non-exposed women [31]. Women of childbearing potential should be advised of the risk of teratogenicity before starting methotrexate treatment. Methotrexate should not be prescribed to women who are considering pregnancy or are unwilling to use effective contraception [32]. Women taking methotrexate who wish to become pregnant have to stop treatment and start taking high doses of folic acid at least three months before conception, and in the meantime continue using effective contraception. In the case of significant intensification of skin lesions during pregnancy, phototherapy, which is safe in pregnancy, may be a good alternative to systemic medications [27].

In the treatment of IBS, drugs are used that have a documented effect on the reproductive capacity of men and women. The therapy usually begins at the time of diagnosis, which is usually between 20 and 30 years of age - which in the period of the greatest fertility of a human being [33].

The most commonly used drug for IBS is mesalazine. Mesalazine, taken by pregnant women, reaches only low levels in the fetal circulation due to poor transplacental transfer and rapid renal excretion. It is not associated with an increased risk of birth defects and is considered safe for use in pregnancy [34]. A meta-analysis did not reveal an increased risk of preterm labor, spontaneous abortion, stillbirth or congenital anomaly after administration of 5-ASA during pregnancy. Mesalazine is considered safe for pregnant women in doses up to 3 g/day [35]. The exception is 5-ASA preparations coated with dibutyl phthalate (DBP), which is involved in inducing abnormalities in the genitourinary system and skeleton in animals and in dysregulation of thyroid and reproductive hormones in humans [36]. 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 [37].

Glucocorticosteroids are used in the treatment of IBS, especially exacerbations. Corticosteroids can cross the placenta where they are rapidly metabolised by the enzyme 11-β-hydroxysteroid dehydrogenase

type 2 to less active metabolites, thus reducing fetal exposure. The shorter-acting forms, such as prednisolone and methylprednisolone, are metabolized faster and more intensively than the longer-acting preparations such as dexamethasone, 98% of which pass intact through the placenta to reach higher levels in the fetus. The levels of endogenous glucocorticosteroids in the fetal circulation are much lower than in the maternal circulation, which makes the fetus more susceptible to iatrogenic corticosteroids. Many studies have identified an increased risk of maternal and fetal complications from the use of corticosteroids during pregnancy. These include gestational diabetes mellitus, preterm labor, LBW, and neonatal adrenal suppression [38, 39]. However, given that these drugs are generally reserved for patients with active disease, it is difficult to distinguish whether observed side effects are secondary to active exposure to IBD or corticosteroids.

It should also be mentioned that in the presence of IBS and psoriasis, systemic glucocorticosteroids are drugs that negatively affect psoriasis and can exacerbate the disease [40].

Thiopurines, which include mercaprotuprine and azathioprine, are drugs used in the treatment of IBS. Azathioprine and mercaptopurine can cross the placenta, reaching up to 5% of maternal concentrations in fetal blood samples. The use of thiopurines during pregnancy has been associated with an increased risk of birth defects in animal studies [41], but they are considered safe in humans. This is despite the Food and Drug Administration's Category D pregnancy assessment, which was based on early reports of adverse pregnancy outcomes and birth defects in exposed infants who were complicated by maternal disease and not recently reviewed [42]. Human studies have shown no significant increased risk of birth defects, spontaneous abortion, LBW, or neonatal infection [43].

The new drugs used in the treatment of psoriasis and IBS include biological drugs. Biologics are transplacental transport after 20 weeks of gestation (except certolizumab) and increase the potential risk of fetal adverse events.

Certolizumab pegol is the only biological drug with a confirmed safety profile during pregnancy and lactation. Conclusions were drawn from the analysis of the structure of the molecule and on the basis of data collected from 528 pregnant and breastfeeding patients. There was no teratogenic effect of certolizumab pegol compared to the general US and EU population, and no increased fetal mortality [44]. The 2019 NICE recommendations indicate that certolizumab pegol can be used before and during pregnancy if clinically needed. Patients' representatives indicated that women who are pregnant or planning to become pregnant readily use systemic treatment that can be used throughout pregnancy and breastfeeding.

Adalimumab and infliximab are recombinant human monoclonal antibodies which are immunomodulatory through high affinity for TNFalpha. Drugs are used in the treatment of severe psoriasis and IBS. In Poland, adalimumab is classified as category B according to FDA. This means that the drug should be administered during pregnancy only when absolutely necessary. The available literature data suggest a low risk of use during pregnancy. However, the long-term consequences of intrauterine exposure remain unknown, especially with regard to immune system development and function. In a study in which 100 pregnancies were exposed to adalimumab, infliximab and certolizumab pegol, no adverse effects on pregnancy were found. Moreover, 500 women from the PIANO registry were exposed to anti-TNF alpha during pregnancy: 260 to infliximab, 150 to adalimumab, 65 to certolizumab pegol and 29 to other drugs [45].

There was no increased risk of congenital malformations compared to the non-exposed IBD cohort. A systematic review of over 1,500 pregnancies exposed to anti-TNF did not find any patterns of adverse pregnancy outcomes or birth defects [46].

It has been reported that combination therapy with anti-TNF and thiopurine may be associated with a higher risk of preterm labor [47].

Conclusion

Psoriasis and inflammatory bowel disease usually appear at early age in young people. The reproductive

capacity of people with psoriasis and IBD may be limited compared to the healthy human population, moreover, women with active IBD and/or psoriasis have an increased risk of complications in pregnancy, so keeping the disease in remission is of great importance to optimize maternal and fetal health. Most systemic drugs are contraindicated when trying for a pregnancy, during pregnancy and during breastfeeding. Some of the biological drugs appear to be a safe alternative for women with psoriasis and/or IBS flare-ups while pregnant or breastfeeding, but much research is needed to bring these drugs to the market. It would be advisable to establish an algorithm for the treatment of people with psoriasis, IBS, who have problems with infertility. The cooperation of gynecologists, dermatologists and gastroenerologists is necessary.

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