

Menstrual cycle abnormalities in women with inflammatory bowel disease and effects of biological therapy on gynecological pathology

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Specialty type: Medicine, research and experimental

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Filipec Kanizaj T, Croatia; Knudsen T, Denmark

Received: March 27, 2023

Peer-review started: March 27, 2023

First decision: May 31, 2023

Revised: June 14, 2023

Accepted: June 30, 2023

Article in press: June 30, 2023

Published online: July 26, 2023



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Abstract

Inflammatory bowel disease (IBD) is a chronic condition that affects young individuals in their reproductive years. It may have long-term implications on their reproductive, sexual, and mental health. IBD has been related to menstrual abnormalities. Furthermore, the administration of biological therapy can also result in gynecological issues in addition to the disease itself. The purpose of this review was to present potential menstrual cycle problems in patients with IBD, as well as the impact of adalimumab and other anti-tumor necrosis factor medications on gynecological pathology.

Key Words: Menstrual disorders; Inflammatory bowel disease; Adalimumab; Infliximab; Anti-tumor necrosis factor- α

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Core Tip: In this review, our aim was to present possible menstrual disorders in patients with inflammatory bowel disease (IBD) and the effects of adalimumab and other anti-tumor necrosis factor (TNF) drugs on gynecological pathology. The correct diagnosis and selection of treatment for women with IBD and gynecological disorders can be a challenge for clinicians and can require a more careful and extensive examination of the patient. Furthermore, new studies show the possible widening use of biological therapies, such as reducing ovarian ischemia, preserving ovarian reserve, and reducing the degree of endometriosis. More detailed human studies are needed, as well as studies involving other anti-TNF- α drugs, to clarify their potential benefits in treating these conditions.

Citation: Malinauskiene V, Zuzo A, Liakina V, Kazenaite E, Stundiene I. Menstrual cycle abnormalities in women with inflammatory bowel disease and effects of biological therapy on gynecological pathology. *World J Clin Cases* 2023; 11(21): 4989-4995

URL: <https://www.wjgnet.com/2307-8960/full/v11/i21/4989.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v11.i21.4989>

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic condition that affects young individuals in their reproductive years[1]. IBD may have long-term implications on the reproductive, sexual, developmental, and mental health of those affected, so clinicians who treat IBD in women should emphasize this concern. Although population-based studies showed that the rate of infertility among patients with IBD is comparable to the incidence in the general population[2], psychological issues and mechanical complications caused by surgeries can affect fertility in women with IBD. Furthermore, Crohn's disease (CD) has been associated with menstrual abnormalities[3]. In rare cases, the administration of biological therapy, which is now frequently used in the treatment of IBD, can also result in gynecological abnormalities in addition to the disease itself. Menstrual disorders are described as potentially unusual adverse effects associated with the use of infliximab or adalimumab. However, there are relatively few case studies or reports that discuss how to treat and diagnose these conditions.

In addition, tumor necrosis factor- α (TNF- α) inhibitors, which are commonly used in the treatment of IBD, may be related to menorrhagia and may affect endothelial cell growth, function, and vessel remodeling in the uterus. Elevated production of pro-inflammatory mediators is believed to play a key role in the manifestation of the circumstances leading to polycystic ovarian syndrome or irregular uterine bleeding[4]. Furthermore, the TNF- α inhibitor adalimumab has been linked in several cases to reproductive diseases in women, such as irregular menstruation[5-7].

However, several animal studies have provided new information on the benefits of biological therapy for endometriosis and reproductive function[8-10].

The purpose of our review was to present potential menstrual cycle problems in patients with IBD and to discuss the impact of adalimumab and other anti-TNF drugs on gynecological pathology. Currently, there are no data available on different biologic treatments, including vedolizumab, ustekinumab, or the small molecule Janus kinase inhibitor tofacitinib and menstrual cycle.

LITERATURE SEARCH

An electronic search of the global literature on menstrual disorders in patients with IBD and the effects of anti-TNF- α drugs on gynecological pathology was performed. The scientific literature was searched using the PubMed, Medline, and Web of Science information search systems. The period from which publications were collected was 1995-2023.

The search used the following keywords and their compounds: Menstrual cycle changes in CD patients; menstrual cycle changes in ulcerative colitis (UC) patients; anti-TNF- α and menstruation; effect of adalimumab on gynecology; effect of adalimumab on menstruation; effect of infliximab on gynecology; effect of infliximab on menstruation.

A total of 938 articles and abstracts met the initial search criteria. Of the 938 articles, 72 were chosen for full-text review. As many as 13 articles met the eligibility criteria and were included in the final review (Tables 1-3).

Studies were considered eligible if they met the following criteria: (1) The article meets the purpose of the review; and (2) the article is written in English.

The exclusion criteria were as follows: (1) No full article available; (2) studies of children with primary amenorrhea; (3) studies analyzing the relationship between pregnancy and IBD; and (4) studies analyzing the effect of anti-TNF- α on pregnancy.

IBD AND THE MENSTRUAL CYCLE

The most prevalent issue in adult women with IBD appears to be irregular menstrual cycles, including oligomenorrhea, secondary amenorrhea, and abnormal uterine bleeding, including menorrhagia and metrorrhagia. A study found that almost 60% of IBD patients reported experiencing these abnormalities[11]. Few studies focused on the menstrual cycle

Table 1 Inflammatory bowel disease and menstrual abnormalities

| Ref. | Participants (groups) | Main findings of the study | Study conclusions |
|---|---|---|--|
| Weber <i>et al</i> [11], 1995 | 662 women, who had undergone surgery for IBD: 360 CD; 251 UC; 47 of indeterminate type. 4-unknown | (1) Menstrual abnormalities were reported by 58% of women; (2) Symptomatic vaginal discharge, reported by 40%, was more likely to occur in CD than in UC; (3) Infertility was reported by 25% of women; and (4) 117 (18%) had undergone hysterectomy, 52 (44%) at 35 yr or under | (1) Menstrual abnormalities were commonly reported including oligomenorrhea, menstrual periods longer than 3 mo apart, polymenorrhagia, menstrual periods more frequently than every 3 wk, menorrhagia, periods lasting longer than 7 d; metrorrhagia, bleeding between periods; dysmenorrhea, painful periods requiring treatment and irregular menses; and (2) More hysterectomies were performed in women with inflammatory bowel disease, frequent menstrual abnormalities, chronic abdominal and pelvic pain, and in those undergoing of various abdominal operations |
| Lim <i>et al</i> [18], 2013 | 47 women with IBD: 13 CD; 27 UC; 7 intestinal Bechter disease. 44 women in the control group | (1) IBD group had significantly more frequent gastrointestinal symptoms, such as nausea (30% <i>vs</i> 7%), flatulence (53% <i>vs</i> 22%), and abdominal pain compared to controls; (2) The IBD group experienced more frequent systemic premenstrual symptoms (79% <i>vs</i> 50%), more severe abdominal pain, and lower mean general condition scores during the menstrual period; and (3) Patients with IBD experienced more frequent premenstrual gastrointestinal symptoms than controls, but their symptoms of IBD did not change significantly during the menstrual cycle | IBD patients were more likely to report PMS and GI symptoms than healthy women, without exacerbating disease-specific symptoms |
| Saha <i>et al</i> [12], 2013 | 54 women with CD; 66 women in the control group | (1) The prevalence of dysmenorrhea was 40% in cases and 46% in controls; (2) Pain scores were significantly higher in subjects with dysmenorrhea compared to those without between cases and controls; and (3) In women without dysmenorrhea, more controls used pain relievers for menstrual pain | (1) Dysmenorrhea in women with CD was associated with increased use of pain medications for menstrual pain, but not with higher NSAID use; and (2) Prevalence of dysmenorrhea is lower in the CD group than in controls |
| Saha <i>et al</i> [13], 2014 | 121 women with IBD: 61 CD; 48 UC; 12 indeterminate type | (1) 25% of subjects experienced a change in the cycle interval in the year before the diagnosis of IBD and 21% experienced a change in the duration of flow; and (2) Among women with dysmenorrhea, 40% experienced a change in the intensity of menstrual pain and 31% experienced a change in its duration | (1) Changes in menstrual function occur frequently in the year before IBD diagnosis; (2) Screening for menstrual irregularities should be considered in women with newly diagnosed IBD; and (3) Cycles typically become more regular over time |
| Lahat <i>et al</i> [15], 2020 | 139 patients with IBD: 100 CD; 39 UC. 258 in the control group | (1) Smoking status was found to be associated with various symptoms during menses in patients with IBD, including a higher level of irritability, nausea, lower back pain, and nervousness; (2) During the premenstrual period, patients receiving biologic treatment reported significantly higher levels of irritability, swelling of the legs, and fatigue; (3) There was no difference in the frequency of pain between patients with CD and UC; and (4) Patients with IBD experience more frequent systemic symptoms during menses than controls | (1) Patients with IBD experience various symptoms during menses significantly more frequently than healthy women; and (2) Smoking, biologic treatment, and previous abdominal operations are risk factors for increased symptomatic burden |
| Shirwaikar Thomas <i>et al</i> [17], 2020 | 75 women with IBD: 59 CD; 16 UC | (1) Patients with lower menstrual distress scores had a higher quality of life; and (2) There were no statistically significant differences in MDQ in patients on biologic or conventional therapies; and (3) No statistically significant correlation between MDQ and endoscopic score | The severity of menstrual symptoms is associated with a poorer quality of life among women with IBD. However, this may not reflect the true severity of the disease |

IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; MDQ: Mayo dysphagia questionnaire.

and symptoms in women with IBD.

In total, Weber *et al*[11] interviewed 662 female patients who had undergone IBD surgery[11]. 58% of the respondents reported an irregular period, including 30% of women with CD. Furthermore, 22% of those with UC had oligomenorrhea or menstrual cycles that were more than 3 mo apart. In 23% of CD-suffering women and 15% of UC-suffering women, menstrual cycles were observed that were more frequent than every 3 wk. 25% of women with CD and 23% of women with UC reported menorrhagia, or periods that lasted more than 7 d. Furthermore, 28% of the CD patients and 22% of the UC patients had metrorrhagia or bleeding between periods. Dysmenorrhea and painful periods requiring medical attention were reported in 24% of CD cases and 20% of UC cases. Menstrual irregularities were observed in 29% of CD cases and 28% of UC cases[11].

However, a study by Saha *et al*[12,13] showed that the prevalence of dysmenorrhea was lower in the IBD group than in the control. These differences between the studies may be due to different populations analysed: Weber *et al*[11] focused on patients generally with IBD while Saha *et al*[12,13] focused on patients with CD. In another study by Saha *et al*[12,13], in the year before receiving an IBD diagnosis, 21% and 25% of the subjects exhibited changes in flow duration and cycle

Table 2 Anti-tumor necrosis factor and gynecology in animal studies

| Ref. | Title | Animal | Main findings |
|----------------------------------|--|--------|--|
| Kaplan and Türk[9], 2020 | Adalimumab Increases Follicle Reserve and Follicle Development in Rat Ovary: The Effect of Adalimumab on Ovarian Reserve | Rats | (1) Ovarian follicle count and AMH level were significantly higher in the groups given adalimumab; and (2) Fibrosis decreased proportionally to the dose of adalimumab |
| Beyazit <i>et al</i> [8], 2019 | Adalimumab mitigates ovarian ischemia-reperfusion injury in rats by regulating oxidative stress, apoptosis, and resolution of inflammation | Rats | (1) Total oxidant status of the tissue, the oxidative stress index, and the values of nitric oxide were significantly decreased, and the total antioxidant status of the tissue was found to increase in the group receiving adalimumab; (2) Inflammation, vascular congestion, and hemorrhagia were significantly lower in adalimumab-treated group; and (3) Adalimumab treatment significantly decreased the apoptotic index |
| Kaplan <i>et al</i> [10], 2022 | The effects of adalimumab on the rat autotransplantation endometriosis model: A placebo-controlled randomized study | Rats | After adalimumab treatment, the average size of the endometriotic implant decreased compared to the control group |
| Falconer <i>et al</i> [33], 2006 | Treatment with anti-TNF monoclonal antibody (c5N) reduces the extent of induced endometriosis in the baboon | Baboon | Significant reductions in total surface area, estimated total volume of endometriotic lesions, and both number and surface area of red lesions were observed after infliximab treatment, but not after placebo treatment |

TNF: Tumor necrosis factor.

Table 3 Anti-tumor necrosis factor and gynecology: Case reports

| Ref. | Disease | Findings |
|---------------------------------|---|---|
| Bes and Soy[6], 2012 | Ankylosing spondylitis | Menorrhagia associated with the use of adalimumab |
| Scheinfeld[5], 2008 | Psoriatic arthritis, psoriasis vulgaris | Menorrhagia and severe abdominal pain associated with the use of adalimumab |
| Katsanos <i>et al</i> [7], 2010 | Crohn's disease | Menorrhagia associated with the use of adalimumab |

interval, respectively[12,13].

It is significant to note that while IBD and dysmenorrhea share many symptoms, it can be challenging to distinguish them. Individuals with both illnesses frequently experience diarrhea, mood fluctuations (irritability, depression), nausea, and vomiting[14]. It is even more challenging to identify the exacerbation of IBD, since acute symptoms possibly include dysmenorrheal symptoms. The pathophysiological mechanisms of prostaglandins may be a contributing factor to dysmenorrhea in women with IBD[15]. Although prostaglandins are known to be associated with inflammatory processes in IBD, it can be painful and uncomfortable when the endometrium secretes them in large amounts. Premenstrual prostaglandins cause the smooth uterine muscles to contract, causing the cramping that many women associate with menstruation. Patients experience diarrhea and stomach pain due to the effects of prostaglandins on intestinal smooth muscle contraction and electrolyte secretion[15,13]. Another mechanism is related to how estrogen affects the gastrointestinal system (GI). Estrogen receptors have been established to line the GI system and estradiol injections can alleviate stomach pain, according to a trial[15,16].

In one study, researchers discovered that 40% of the CD patients who participated in the study experienced severe pain and complained of dysmenorrhea[12]. Menstrual symptoms may make it more difficult for a patient to perceive the activity of IBD, according to the positive correlation between CD activity levels and the menstrual distress questionnaire distributed in the study[12].

In a study by Shirwaikar Thomas *et al*[17], patients with lower menstrual distress scores had better quality of life for IBD[17].

In one prospective trial, researchers looked at how women's symptoms specific for and nonspecific for IBD changed during the menstrual cycle. Compared to the premenstrual and postmenstrual phases, the menstrual period was marked by greater abdominal discomfort for both the patient and the control groups. Compared to the control group, the patient group reported looser stools and more frequent feces, as well as more severe abdominal pain[18].

Another study assessed the severity of GI symptoms in patients with IBD who underwent biological therapy *vs* traditional treatments during menstruation. There were no discernible differences between the two groups of patients [17].

Clinicians should be aware of the potential impact of the cycle phases when assessing the cyclical aggravation of GI symptoms[17]. To improve women's health during menstruation, treatment options should be used to reduce the cyclical aggravation of symptoms of IBD.

A study by Lahat *et al*[15] identified risk factors in people with IBD, leading to worsening of symptoms during both the premenstrual phase and menstruation. Smoking was found to significantly worsen premenstrual symptoms including nervousness, lower back pain, nausea, and fatigue[15].

TNF- α BLOCKING AGENTS AND GYNECOLOGICAL MANIFESTATIONS

Adalimumab, a tumor necrosis factor alpha inhibitor, is a drug that is frequently used in the treatment of many inflammatory diseases. The Food and Drug Administration initially approved it for the treatment of rheumatoid arthritis[19]. Adalimumab is now authorized for the treatment of several different disorders, including rheumatoid arthritis, ankylosing spondylitis, CD, and UC[20]. The main side effects of Adalimumab include infections, lupus-like disease, and others[20]. Menstrual abnormalities are listed as potential, infrequent adverse effects of taking adalimumab, and there are relatively few case studies that discuss how to treat them[21].

In one published case report, a woman who used adalimumab and experienced menorrhagia and dysmenorrhea was described. When oral contraceptives were administered to the patient, menorrhagia and menstrual discomfort were reduced to manageable levels[5]. Another study presented a similar case, where adalimumab caused menorrhagia that was relieved by prescribing oral contraceptives[7]. Some studies have shown that TNF- α levels are crucial to maintaining a normal menstrual cycle, as they are significantly higher during the menstrual phase than during the luteal phase[22].

Moreover, TNF- α may also induce apoptosis and cell dissociation in the endometrium, resulting in menstrual shedding and excessive bleeding, according to another mechanism[23]. TNF- α and other inflammatory mediators have been administered in several trials, and as a result, endometrial bleeding and vascular injury have been observed. This evidence suggests that TNF- α administration may cause significant uterine bleeding[7,24].

In particular, adalimumab has been found to restore menstruation in premature ovarian failure, in addition to causing atypical menstrual bleeding. One case included a patient with adalimumab prescription. Her doctor administered a combination of progesterone and estrogen to prevent osteoporosis 20 mo before the start of adalimumab treatment because her menstrual cycle had completely stopped. The patient had menopausal-specific hormone levels, including significantly lower levels of estradiol and androgen and higher levels of follicular stimulating hormone. Her menstrual cycle returned 3 mo after the administration of adalimumab, and hormone therapy was discontinued[21].

THE EFFECTS OF ADALIMUMAB ON OVARIAN ISCHEMIA

When the ovary and fallopian tubes twist over the ligaments that link them to the adnexa, this results in a pathological phenomenon known as ovarian torsion. This urgent condition frequently appears in the first 30 years of life. Patients who have abdominal or pelvic pain, which may be intermittent if the ovary is torsioning or detorsing, present with nonspecific clinical symptoms. Some patients experience nausea and vomiting; in more severe cases, fever occurs, as in the case of ovarian necrosis. It is crucial to recognize this condition as soon as possible and to provide appropriate therapy to minimize probable necrosis and prevent infertility. Usually, diagnosis is challenging because imaging and laboratory results are typically normal or nonspecific. Laparoscopic surgery or a laparotomy to reestablish blood flow is the primary treatment. However, ovarian atrophy and necrosis are frequent results of delayed diagnosis of this condition[8,25].

Adalimumab may be clinically beneficial in the management of ovarian ischemia caused by ovarian torsion[26]. To reduce the inflammatory mediators released during ischemia and reperfusion, researchers evaluated the therapeutic effect of adalimumab on ovarian injury in rats[8]. The primary inflammatory mediator, TNF- α , which initiates degenerative tissue processes that result in edema and necrosis, is released at the start of ischemia and reperfusion[8,26]. The anti-inflammatory and anti-apoptotic properties of adalimumab were determined by examining biochemical and histological alterations in rats with ovarian ischemia. According to the findings, adalimumab suppressed inflammatory processes in rats at the molecular level[8]. Adalimumab treatment resulted in reduced levels of inflammatory markers such as TNF- α and interleukin 1 beta and provided therapeutic effects on edema and vascular congestion at the histological level. Inflammatory processes and oxidative stress decreased, possibly due to the pharmacodynamic action of the drug[8].

Today, all data on the effects of adalimumab on ovarian ischemia are limited to animal studies. Human studies are needed to provide more information on the possible effect of anti-TNF drugs on ovarian ischemia.

THE EFFECTS OF ADALIMUMAB ON OVARIAN RESERVE AND FIBROSIS

In one trial, the effects of adalimumab on ovarian reserve and fibrosis were investigated in rats. Adalimumab was administered at low and high doses, and the number of follicles in the ovaries increased, according to an analysis of biochemical and histological changes[9]. Administration of a larger dose of adalimumab also had a substantial impact on the level of Anti-Müllerian hormone, which is crucial to assess the reserve function of the ovaries[9,27].

In addition, ovarian fibrosis was examined to see whether adalimumab had altered it. Ovarian fibrosis is a serious illness that alters ovarian function and has an adverse effect on women's quality of life and reproductive health. The physiological functions of the ovaries are altered as ovarian fibrosis progresses, leading to premature ovarian failure[9, 28]. Adalimumab treatment for ovarian fibrosis in rats resulted in a decrease in fibrosis. Inhibition of these inflammatory mediators by adalimumab allowed successful treatment results, as the inflammatory processes of the ovaries create TNF- α and other inflammatory cytokines[9].

More studies are required to understand these physiological mechanisms in relation to ovarian reserve and reduction of fibrosis considering the beneficial effects of adalimumab in these areas. Adalimumab may now have a wider range of therapeutic applications, including the treatment of premature ovarian failure in women with inflammatory disorders and the preservation of female reproductive function after pelvic surgery.

THE EFFECTS OF ANTI-TNF DRUGS ON ENDOMETRIOSIS

Endometriosis is a painful disorder in which endometrial tissue grows outside the uterus, covering the ovaries, fallopian tubes, and other pelvic tissues. Its prevalence varies from 5% to 10% in women[10,29]. In many cases, women with endometriosis have difficulty conceiving and experience abdominal and menstrual pain[10,30].

The beneficial impact of adalimumab in reducing endometriosis levels has been reported in animal studies[10].

In one study, rats affected by endometriosis were given adalimumab and the results were analyzed with respect to changes in histological and biochemical characteristics. Macroscopic and histological evaluations revealed a decrease in endometrium tissue. When evaluating biochemical markers, it was found that adalimumab treatment caused the concentration of fibrillin-1, a fibrosis indicator, to drop. Adalimumab is believed to have reduced endometriosis by suppressing TNF- α and other inflammatory factors because they are cytokines involved in the etiology of endometriosis[10].

This trial demonstrated the anti-inflammatory effects of adalimumab on histological alterations of endometriosis and a decrease in fibrosis in rats. Since most of the data come from animal studies, there is a major knowledge gap in this area and more studies are needed.

The evaluation of the impact of infliximab on pain reduction in women with profound endometriosis produced some interesting results. TNF- α medication was expected to considerably decrease pain in endometriosis patients, since inflammation is related to the pathophysiology of the condition. According to the findings of a study, only 30% of individuals who received infliximab experienced pain relief[31]. This finding was comparable to the results in the placebo group. No discernible reduction in endometriosis was observed with infliximab administration when evaluating the degree of endometriosis at the time of surgery[31]. It is likely that treatment was ineffective because the etiologies of superficial and deep endometriosis pain are different[28,31,32].

Upon examination of other anti-TNF- α drugs, the authors found that the administration of an anti-TNF- α monoclonal antibody (C5N) had positive therapeutic effects in reducing endometriosis in baboons. The findings of one study demonstrated that, compared to the control group, anti-TNF- α C5N reduces both the extent of the damage and the area affected by endometriosis. The menstrual cycle had not been disrupted when the baboons received therapy. Therefore, these trials can serve as a crucial starting point in the search for an effective method of treating human endometriosis[33].

CONCLUSION

It is difficult for clinicians to make the correct diagnosis and select the best course of treatment for women with IBD and gynecological diseases. It is crucial to perform a more detailed examination and to take a more holistic approach with patients who have both conditions, because their symptoms may overlap or do not signify the progression of these diseases. Furthermore, new research indicates that biological therapy may be used more widely than previously thought, and additional research is required to determine the safety and efficacy of its application for humans.

FOOTNOTES

Author contributions: Malinauskiene V and Zuzo A performed a literature search and wrote a manuscript draft; Kazenaite E, Liakina V, and Stundiene I revised the sources of the literature and the text of the manuscript; All authors have read and approved the final version of the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Fan JR

L-Editor: A

P-Editor: Fan JR

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