Impact of Menopause and Clinical Considerations in Patients With Inflammatory Bowel Disease

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Abstract: Menopause is marked by a natural decline in estrogen and progesterone that alters gut barrier integrity, immune regulation, and systemic inflammation. In women with inflammatory bowel disease (IBD), this interplay may result in increased symptoms and worse clinical outcomes. Women with IBD face diagnostic delays, distinct disease phenotypes, higher rates of extraintestinal manifestations, and greater treatment burden. In menopausal women with IBD, specific guidance remains scarce. Beyond gut-specific effects, menopausal women are at an increased risk of osteoporosis, cardiovascular disease, and mood disorders. Lacking is a framework that promotes individualized, multidisciplinary care for menopausal women with IBD, focusing on the alterations in the immune system, gut microbiome, clinical presentations, multisystem risks, and therapeutic considerations. This article aims to synthesize the current evidence and research gaps around the impact of menopause in IBD, evaluate the safety and effectiveness of menopausal hormone therapy in this context, and propose a practical, patient-centered management framework for clinicians.

Keywords
Inflammatory bowel disease, Crohn's disease, ulcerative colitis, menopause, perimenopause, estrogen, progesterone, hormone therapy

Menopause is a retrospective diagnosis defined as 12 months of amenorrhea or following surgical removal of both ovaries.[1,2] The average age of menopause in the United States is 52 years, with 90% of women experiencing it between the ages of 45 and 58 years.[3,4] Perimenopause is the period leading up to menopause and is characterized by a decline in ovarian function, fluctuating hormone levels, and irregular menstrual cycles, through 12 months after the final menstrual period.[5-7] Both perimenopause and menopause are marked by vasomotor symptoms (hot flashes and night sweats), mood changes, sleep disturbance, and genitourinary symptoms.[8,9]

Inflammatory bowel disease (IBD), encompassing ulcerative colitis (UC) and Crohn's disease (CD), is a chronic, immune-mediated disorder of the gastrointestinal (GI) tract characterized by relapsing and remitting inflammation.[10] UC is confined to the colon, whereas CD can involve any portion of the GI tract and is frequently associated with transmural inflammation.[11,12] The etiology of IBD remains incompletely understood but appears to be related to complex interactions involving genetic susceptibility, environmental triggers, immune dysregulation, and alterations in the gut microbiome, resulting in an exaggerated intestinal inflammatory response in vulnerable individuals.[12] Over the past few decades, there has been a rise in the incidence of IBD globally, with older individuals (age >60 years) now representing the largest growing patient population with IBD.[13-15] Symptoms of active disease can vary based on disease location but can include abdominal pain, diarrhea, urgency, incontinence, rectal bleeding, weight loss, and fatigue.[16] Variability in clinical presentations of IBD and prognosis, especially with sex-based differences, poses a challenge in generalizing the existing treatment strategies. Women face diagnostic delays with higher rates of misdiagnosis at all health care levels.[17-20]

The hormonal and physiologic changes of perimenopause and menopause affect multiple organ systems, including the GI tract.[21] Understanding the interaction between IBD and menopause is critical to identify clinical presentations, anticipate health risks, optimize care, and ensure appropriate counseling for women both at risk of and already living with IBD during midlife. This article highlights key knowledge gaps and important clinical considerations in the management of IBD in women transitioning through and beyond menopause.

Literature Search Strategy and Study Selection

The evidence on the effects of menopause in women with IBD summarized in this article is from a comprehensive literature search of PubMed/MEDLINE performed using a combination of search terms. These include IBD (CD and UC), menopause (perimenopause and postmenopause), estrogen, progesterone, hormone replacement therapy and hormone therapy, gut microbiome, bone health, cardiovascular disease, and quality of life. Peer-reviewed original research articles, systematic reviews, meta-analyses, clinical practice guidelines, and observational studies published in English that addressed the intersection of menopause and IBD are included. Although human clinical studies are prioritized, experimental and animal studies are included when they provide mechanistic insights that are relevant to the clinical pathophysiology. Among excluded data are case reports, editorials, opinion pieces, and conference abstracts without full-text availability. Emphasis is placed on clinical practice guidelines, randomized controlled trials, and large observational cohort studies. Where high-quality clinical evidence is limited, mechanistic studies or expert consensus is offered to provide context. There is no formal quality assessment or risk of bias evaluation, given the heterogeneity of study designs and exploratory nature of this emerging field; however, level and source of evidence is identified while presenting findings to allow readers to assess the strength of conclusions.

Menopause and Inflammatory Bowel Disease

Menopause and IBD share overlapping clinical features, which can complicate assessment of disease activity and symptom attribution in postmenopausal women (Figure 1). Complicating this further is the fact that symptom severity does not always reflect the inflammatory burden in patients with IBD. Some menopausal women with IBD may have no symptoms but underlying subclinical inflammation. This increases the risk of progression of disease, complications, hospitalizations, and surgeries. Conversely, other menopausal women with IBD may have significant symptoms in the absence of active disease, which can be related to a variety of noninflammatory causes for GI symptoms. When treatment decisions are guided by symptoms alone in this population, there is a potential for both inappropriate therapy escalation in patients with noninflammatory symptoms and inadequate treatment in those with subclinical inflammation. Both menopause and IBD are associated with mood disorders, sexual dysfunction, and reduced quality of life.[22,23] In one study, IBD severity in postmenopausal women was associated with lower quality of life in psychosocial, physical, and sexual domains, although vasomotor symptoms were not significantly affected.[24] Evidence suggests that estrogen and progesterone play central roles in the pathophysiology of chronic inflammatory and degenerative diseases, supporting the hypothesis that hormonal changes during menopause may influence IBD onset, progression, and symptomatology.[25-27] Some studies indicate that menopause can alter IBD clinical presentation and symptom perception by influencing gut motility, visceral sensitivity, and immune function, although findings remain inconsistent.[21,28-32]

Hormonal and Immunologic Impacts During Menopause

Estrogen and progesterone levels fluctuate during perimenopause then decline after menopause, which can

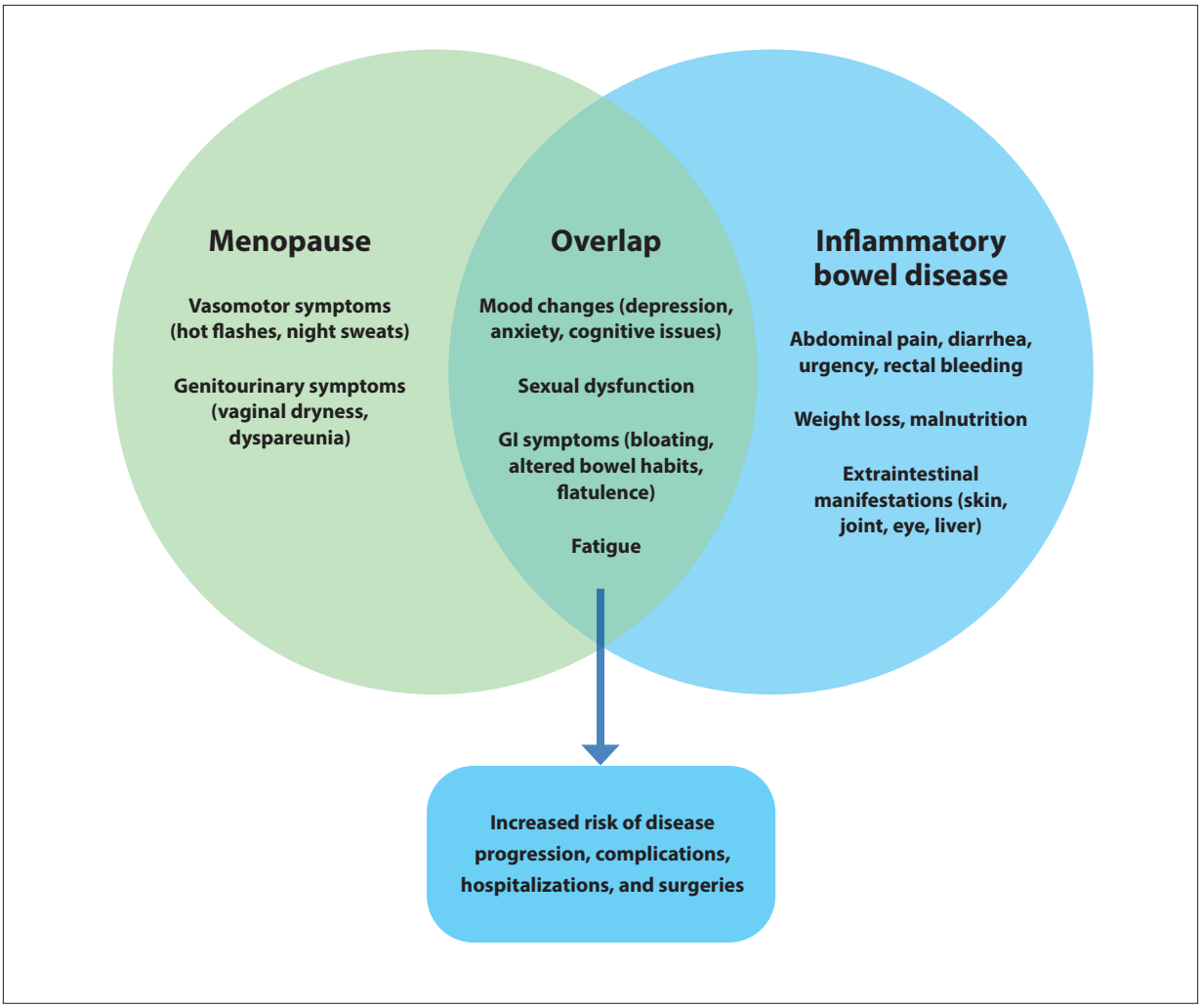

Figure 1. Clinical overlap between menopause and inflammatory bowel disease.

GI, gastrointestinal.

induce a sequence of physiologic changes that extend beyond reproductive health.[33] Experimental data indicate that both hormones protect mucus-secreting intestinal epithelial cells from oxidative injury, enhance tight junction protein expression, and promote mucosal repair, thereby maintaining gut barrier integrity.[34] Human studies have demonstrated that estrogen receptor-β (ERβ) signaling plays an important role in sustaining colonic epithelial barrier function.[35] In addition to preserving barrier integrity, estrogen and progesterone modulate both innate and adaptive immunity. Declining estrogen levels are associated with increased production of proinflammatory cytokines, including interleukin (IL)-6 and tumor necrosis factor (TNF), both central mediators of IBD pathogenesis.[36,37] Estrogen receptors are widely expressed on immune cells, influencing responses to gut microbiota and regulating inflammation.[35] ERβ expression has been found to be significantly reduced in both peripheral T lymphocytes and colonic mucosa of IBD patients with active disease compared with patients in remission, whereas IL-6 has been shown to further downregulate ERβ, perpetuating mucosal inflammation.[35] It has also been noted that ERβ levels normalize in patients responsive to anti-TNF therapy.[35] This suggests that ERβ may serve as a biomarker of disease activity and a potential therapeutic target.

Menopause is also characterized by increased gut permeability, reflected by elevated circulating permeability markers.[38] Declining estrogen and progesterone concentrations weaken intestinal epithelial barrier function, facilitating translocation of microbial products into systemic circulation. This triggers systemic immune activation and sustains a chronic, low-grade inflammatory state, measured by elevated serum proinflammatory cytokines

(IL-6, TNF), high-sensitivity C-reactive protein (CRP), and endotoxin levels.[37-39] In IBD, disease monitoring is most commonly done using serum CRP, fecal calprotectin, and circulating cytokines, including IL-6. Serum soluble IL-2 receptor may serve as an additional marker, particularly reflecting endoscopic remission.[40] In women with IBD who already have baseline barrier dysfunction, these declines in hormonal levels create a self-perpetuating cycle of mucosal injury, immune activation, and inflammation.[38] Together, these findings highlight how hormonal decline during menopause exacerbates immune dysregulation and gut barrier disruption. Women with IBD report lower menopause-related quality of life influenced by disease severity.[24] Although most women experience stable symptoms after menopause, some note worsening and increased hormonal sensitivity. Although supportive of hormonal decline and clinical outcomes, studies that incorporate gut permeability, cytokine profiles, and disease activity across menopause are limited.[4]

Microbiome Dysbiosis in Menopause

The gut microbial composition of postmenopausal women differs from that of premenopausal women and displays reduced diversity, a lower Firmicutes-to-Bacteroidetes ratio, and an increased abundance of proinflammatory bacterial genera.[34,42,43] In clinical studies, these microbial changes are accompanied by elevated proinflammatory cytokines and reduced levels of glucagon-like peptide-1, both of which contribute to systemic inflammation.[43-45] Estrogen deficiency also disrupts microbial metabolic activity, specifically β-glucuronidase function, which impairs estrogen deconjugation and reabsorption through enterohepatic circulation.[46] This leads to accelerated systemic estrogen loss and dysregulated immune function, compounding the estrogen decline caused by ovarian aging and gut dysbiosis.[36,39,44]

Experimental models show that microbial imbalance in menopause is characterized by diminished short-chain fatty acid production, expansion of proinflammatory bacteria species, and immune dysregulation marked by an elevated T helper 17 cell/regulatory T cell ratio and increased IL-17 levels.[47] These changes promote endotoxin production and compromise epithelial barrier integrity, perpetuating a chronic, low-grade inflammatory state.[48,49] Altered signaling through pattern recognition receptors, including toll-like receptors 4 and 5, further amplifies immune instability and susceptibility to inflammatory disease.[49] Interestingly, review articles suggest that hormone therapy (HT) in postmenopausal women is associated with a gut microbial profile resembling that of reproductive-age women, raising the possibility that hormonal interventions may help restore microbial diversity and reduce inflammation in conditions such as IBD.[42,50-52]

Menopause is also associated with GI symptoms including abdominal bloating, increased flatulence, altered bowel habits, and heartburn, many of which can mimic IBD activity and complicate disease assessment.[53] In addition, midlife women report higher rates of pelvic floor dysfunction, anorectal disorders, fatigue, headaches, and anxiety, all of which may intensify the perception and severity of GI symptoms, contributing to diminished quality of life.[54] The overlap of menopause-related changes and IBD pathophysiology may therefore contribute to a higher prevalence and complexity of gut-based symptoms in this population.[21]

Multisystem Considerations in Women With Inflammatory Bowel Disease After Menopause

Women with IBD transitioning through and beyond menopause face multisystem complications driven by estrogen deficiency, chronic inflammation, and medication exposure. Domains that are most significantly influenced include skeletal health, cardiovascular disease risk, and neuropsychiatric well-being (Figure 2). Malignancy risk and medication risks are other important considerations in postmenopausal women with IBD.

Skeletal Health

Both menopause and IBD independently increase the risk of low bone mineral density, categorized as osteopenia or osteoporosis, which can lead to fragility fractures.[55] Approximately one-third of postmenopausal women with IBD meet criteria for osteoporosis, and an additional 40% have osteopenia.[56] Estrogen deficiency accelerates bone resorption and increases fracture risk, whereas systemic inflammation, malnutrition, vitamin D and calcium deficiencies, and long-term corticosteroid use further impair skeletal integrity.[55,57] IBD-associated chronic intestinal inflammation increases production of cytokines, including TNF and IL-6, which stimulate osteoclast activity and suppress bone formation, exacerbating bone loss.[58] Sarcopenia frequently occurs with osteoporosis, often referred to as osteosarcopenia, which worsens clinical outcomes in IBD. Vertebral fractures are particularly common in CD and are strongly associated with advancing age and low body mass index.[59,60] Cumulative corticosteroid use beyond 3 months remains a major contributor to skeletal fragility and bone loss, emphasizing the need for corticosteroid-sparing regimens whenever possible.[55,61,62] The American Gastroenterological Association recommends dual-energy x-ray absorptiometry screening for all postmenopausal women with IBD who have additional osteoporosis risk factors, regardless of age.[63] Use of fracture

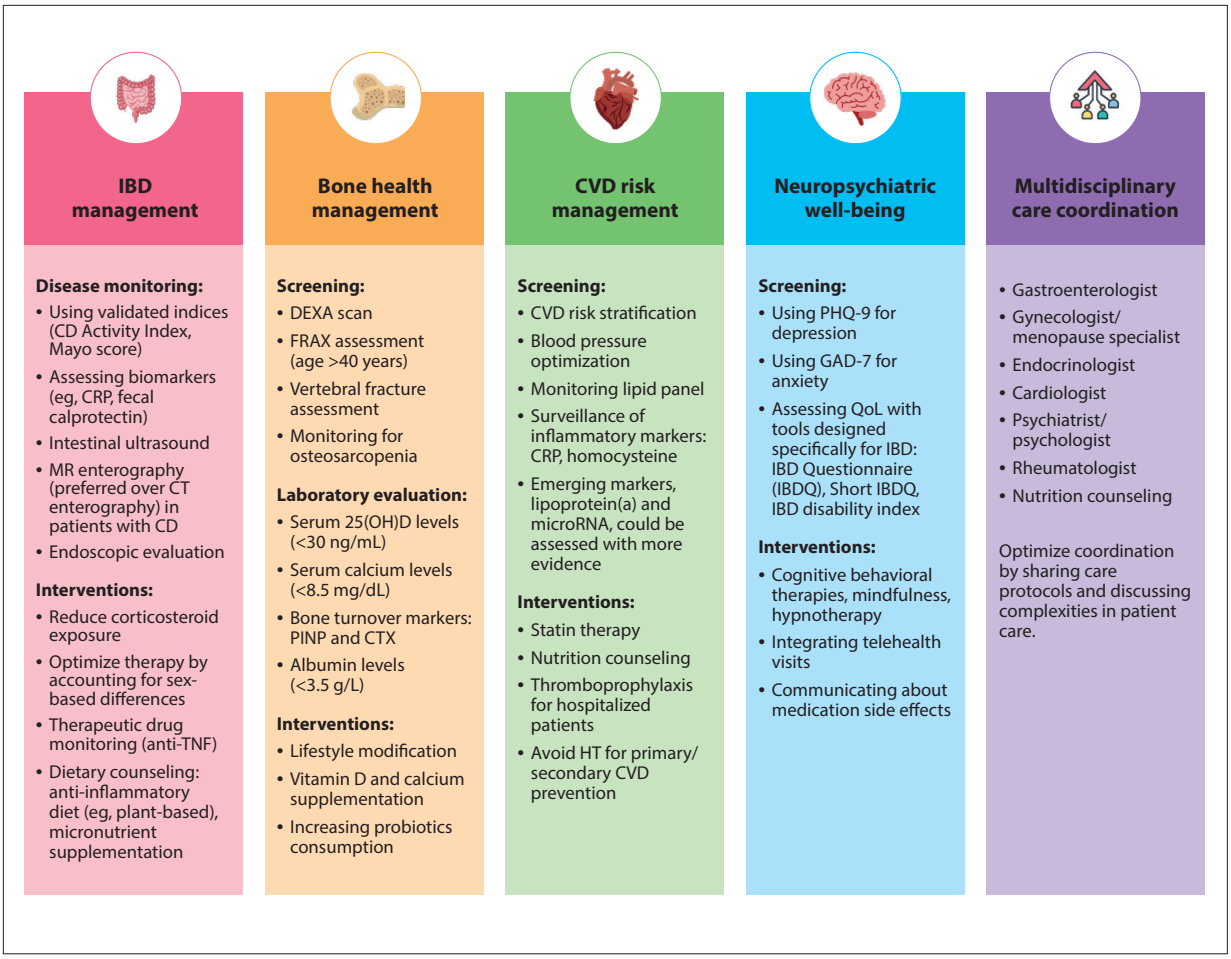

Figure 2. Clinical considerations in managing postmenopausal women with IBD.

25(OH)D, 25-hydroxyvitamin D; CD, Crohn's disease; CRP, C-reactive protein; CT, computed tomography; CTX, C-terminal telopeptide of type I collagen; CVD, cardiovascular disease; DEXA, dual-energy x-ray absorptiometry; FRAX, fracture risk assessment tool; GAD-7, Generalized Anxiety Disorder-7; HT, hormone therapy; IBD, inflammatory bowel disease; MR, magnetic resonance; PHQ-9, Patient Health Questionnaire-9; PINP, procollagen type I N-terminal propeptide; QoL, quality of life; TNF, tumor necrosis factor.

risk assessment tools such as FRAX are recommended for women over 40 years, although optimal screening intervals are not yet established.[63,64] Frequent imaging and monitoring of laboratory results significantly helps physicians treat patients. A serum 25-hydroxyvitamin D level less than 30 ng/mL necessitates supplementation, preferably with calcifediol as it has been shown to have superior efficacy.[65] Calcium supplementation is recommended if total dietary calcium intake is below 1200 mg[66]; however, the initial step is to assess dietary intake before starting supplements. Identifying poor response or nonadherence could be done by monitoring bone turnover markers like procollagen type 1 N-terminal propeptide and C-terminal telopeptide.[67] Additionally, albumin levels less than 3.5 g/dL suggest malnutrition, which can result in increased bone loss and risk of fractures in this population. Optimal treatment includes lifestyle modification (weight-bearing exercise, smoking cessation, and alcohol moderation), calcium (1000-1200 mg/day) and vitamin D (600-800 IU/day) supplementation, and pharmacologic therapy tailored to fracture risk.[66-68] Lastly, meta-analyses and results of a recent randomized, double-blind, placebo-controlled trial suggest that increasing probiotic consumption can cause a modest increase in bone mineral density and reduce bone turnover markers; however, it should be used as adjunctive therapy as data are inconsistent, and further exploration is needed.[69-72]

Cardiovascular and Thromboembolic Risk

Cardiovascular disease risk is significantly elevated in postmenopausal women with IBD. Age-adjusted analyses demonstrate a 41% higher risk of ischemic stroke in

women with IBD compared with those without IBD, along with higher rates of ischemic heart disease and premature atherosclerotic cardiovascular disease.[73,74] IBD is characterized by elevated CRP, homocysteine, oxidized low-density lipoprotein cholesterol, fibrinogen, matrix metallopeptidases, nuclear factor κB, and interferon-γ levels, all of which promote endothelial dysfunction and accelerate atherosclerosis.[74-76] In addition, altered lipid metabolism, dysregulated microRNA expression, and gut microbiome disturbances contribute to adverse cardiac remodeling and long-term cardiovascular risk.[75,77,78] Patients with active IBD are also at increased risk for arterial and venous thromboembolism (VTE) owing to increased procoagulant factors, platelet activity, and fibrinogen concentrations.[74,77,79] In contrast, endogenous estrogen exerts vasoprotective effects by promoting vasodilation, preserving endothelial integrity, and reducing oxidative stress and cytokine-driven vascular injury.[80] High atherosclerotic burden and vascular stiffening also increases susceptibility of developing ischemic colitis. The loss of estrogen after menopause, combined with age-related vascular stiffening, further amplifies cardiovascular and thrombotic risk in this population.[81] In women with increased risk, preventative strategies should include lifestyle modifications, dietary counseling, regular physical activity, blood pressure optimization, statin therapy (in those with additional risk factors), and thromboprophylaxis only when hospitalized. There is a lack of evidence suggesting cardiovascular risk modification in women with IBD.

Use of HT is intended to help combat moderate to severe menopausal symptoms in select patients and is not recommended for either primary or secondary prevention of cardiovascular disease.[82-84] Data suggesting that HT can be safely used in women with IBD are limited, with a caveat that cardiovascular and oncologic risks are taken into consideration. Of note, HT appears to reduce IBD activity, with studies showing protective effect against flares (hazard ratio, 0.18) and improved Physician Global Assessment scores.[85,86] However, therapeutic use of HT should be weighed against potential risks on an individual basis, and transdermal or nonoral formulations are preferred for women at elevated thromboembolic risk.[83,87,88]

Cancer and Medication-Associated Risks

Menopausal women with IBD have elevated risks of malignancy as a result of disease and medication exposure. Use of Janus kinase inhibitors is linked to increased dyslipidemia and potential malignancy (mainly squamous cell carcinoma). Biologics and immunosuppressive medications have been associated with risk of high-grade cervical intraepithelial neoplasia and cervical cancer.[89] Although there is limited concrete evidence about the association between biologics and cervical/vulvar/anal malignancies, surveillance is indicated as menopause independently increases susceptibility to these cancers. Lastly, long-term corticosteroid use elevates the risk of osteoporosis and bone loss. This is often complicated by polypharmacy and increased risk of drug interactions in older women with IBD, as these patients already have multiple comorbidities and are at an increased risk for cumulative toxicity.[90]

Neuropsychiatric Well-Being

Menopause is associated with increased rates of depression, anxiety, and fatigue, and cognitive difficulties, with up to 65% of women with IBD (aged ≥18 years) experiencing depression and anxiety.[91] These symptoms are thought to arise in part from fluctuating estrogen levels, which affect serotonin and γ-aminobutyric acid signaling pathways involved in mood and stress regulation.[92] Commonly reported issues include memory lapses and concentration difficulties, often referred to as brain fog.[31] Women with IBD are particularly vulnerable owing to overlapping contributors, including chronic systemic inflammation, hypothalamic-pituitary-adrenal axis dysregulation, and disorders of the gut-brain interaction, visible disease manifestations, and corticosteroid side effects, all of which can significantly impair quality of life.[93,94] One systematic review and meta-analysis suggests a bidirectional association between IBD and mood disorders, indicating that depression and anxiety not only result from chronic illness but may also exacerbate disease activity and outcomes.[93] Therefore, routine mental health screening is recommended and may be facilitated by validated instruments such as the Patient Health Questionnaire-9 and Generalized Anxiety Disorder-7.[63] Quality of life can be assessed with tools designed specifically for IBD, including the IBD Questionnaire, Short IBD Questionnaire, and IBD disability index.[95,96] Integration of these screening tools into routine care may enhance early detection, continuity of care, and treatment adherence.[91] Optimizing patient care also involves the integration of cognitive behavioral therapies, mindfulness techniques, and hypnotherapy.[97,98] Furthermore, the utilization of telehealth platforms facilitates continuity of care and effective communication regarding medication adverse effects.

Hormonal Therapy and Inflammatory Bowel Disease

The impact of HT on IBD activity and incidence remains uncertain, with evidence from different studies yielding mixed results. A 2008 retrospective study found that postmenopausal women with IBD who initiated HT shortly after menopause were 82% less likely to have active disease than nonusers, and disease flares in HT users required less

aggressive treatment.[85] Similarly, a 2023 multicenter retrospective cohort study reported that HT use was associated with a 5.6-fold higher likelihood of improvement in Physician Global Assessment scores, a measure of disease activity, compared with controls.[86] Smaller studies also support improved IBD-related outcomes among women receiving HT, likely owing to estrogen's anti-inflammatory properties.[85] However, these studies are limited by retrospective design, small sample sizes, and reliance on subjective measures of disease activity, restricting their generalizability.

In contrast, other studies raise concerns about adverse outcomes associated with HT. In a prospective cohort study of 108,844 postmenopausal women without prior history of IBD enrolled in the Nurses' Health Study, HT use was found to be associated with an increased risk of developing UC but not CD, with the risk increasing with longer HT duration and declining after discontinuation.[99] The previously mentioned 2023 multicenter retrospective cohort study prolonged HT use increased the risk of UC, with hazard ratios of 1.71 for current users and 1.65 for past users, but found no association with CD.[86] Another case-control study of 444 IBD patients and 10,000 controls showed that extended HT and oral contraceptive use were associated with increased odds of CD, whereas smoking and prior appendectomy were inversely associated with UC risk.[100] Conversely, a large population-based cohort study reported no significant association between HT use and IBD incidence in postmenopausal women, highlighting the heterogeneity of findings.[101]

Timing of HT initiation is crucial in determining its risk-benefit profile, with earlier initiation being linked with more favorable outcomes. Data from observational studies and randomized controlled trials, including the Women's Health Initiative, show that starting HT more than 10 years after menopause or after age 60 years increases the risk of VTE, pulmonary embolism, and stroke.[102] Although HT is generally considered safe for healthy women near menopause, its role and implications for IBD patients remain inadequately studied. Given conflicting evidence and limited data, HT decisions in this population should be individualized, with careful consideration of symptom severity, disease activity, contraindications, age, and comorbidities.

Conclusion

Women with IBD face unique challenges during and after menopause owing to hormonal changes that affect gut barrier function, immune regulation, and disease activity, compounded by chronic inflammation and medication effects. This intersection increases the risk of osteoporosis, cardiovascular disease, thromboembolism, medication side effects, and mental health disorders, underscoring the need for individualized, multidisciplinary care. Evidence regarding the impact of HT remains limited and heterogeneous, highlighting the importance of personalized decision-making and further research to guide optimal management and improve quality of life in this population. Figure 2 provides a framework summarizing the key domains of care to help guide physicians through the complex interactions between multisystem vulnerabilities, driven by fluctuating hormones and microbiome alterations, and overall therapeutic management in postmenopausal women with IBD.

Disclosures

Dr Shah, Dr Karam, and Ms Hao have no relevant conflicts of interest to disclose. Dr Shufelt is an advisor for Bayer Pharmaceuticals. Dr Kinnucan is an advisor and consultant to AbbVie, Johnson & Johnson, Lilly, Pfizer, Takeda, and Bristol Myers Squibb.

References

1. Mishra GD, Chung HF, Cano A, et al. EMAS position statement: predictors of premature and early natural menopause. *Maturitas*. 2019;123:82-88.
2. Gold EB, Crawford SL, Avis NE, et al. Factors related to age at natural menopause: longitudinal analyses from SWAN. *Am J Epidemiol*. 2013;178(1):70-83.
3. Zhu D, Chung HF, Pandeya N, et al. Body mass index and age at natural menopause: an international pooled analysis of 11 prospective studies. *Eur J Epidemiol*. 2018;33(8):699-710.
4. Peacock K, Carlson K, Ketvertis KM. Menopause. *StatPearls*. http://www.ncbi.nlm.nih.gov/books/NBK507826/. Updated December 21, 2023. Accessed February 16, 2026.
5. Santoro N. The menopausal transition. *Am J Med*. 2005;118(suppl 12B):8-13.
6. Santoro N, Roeca C, Peters BA, Neal-Perry G. The menopause transition: signs, symptoms, and management options. *J Clin Endocrinol Metab*. 2021;106(1):1-15.
7. Harlow SD, Gass M, Hall JE, et al; STRAW 10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *Menopause*. 2012;19(4):387-395.
8. Avis NE, Stellato R, Crawford S, et al. Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. *Soc Sci Med 1982*. 2001;52(3):345-356.
9. Gold EB, Colvin A, Avis N, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. *Am J Public Health*. 2006;96(7):1226-1235.
10. Rocchi A, Benchimol EI, Bernstein CN, et al. Inflammatory bowel disease: a Canadian burden of illness review. *Can J Gastroenterol*. 2012;26(11):811-817.
11. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature*. 2007;448(7152):427-434.
12. Podolsky DK. Inflammatory bowel disease. *N Engl J Med*. 2002;347(6):417-429.
13. Vieujean S, Caron B, Jairath V, et al. Is it time to include older adults in inflammatory bowel disease trials? A call for action. *Lancet Healthy Longev*. 2022;3(5):e356-e366.
14. Windsor JW, Kaplan GG. Evolving epidemiology of IBD. *Curr Gastroenterol Rep*. 2019;21(8):40.
15. Nguyen GC, Targownik LE, Singh H, et al. The impact of inflammatory bowel disease in Canada 2018: IBD in seniors. *J Can Assoc Gastroenterol*. 2019;2(suppl 1):S68-S72.
16. Devlen J, Beusterien K, Yen L, Ahmed A, Cheifetz AS, Moss AC. The burden of inflammatory bowel disease: a patient-reported qualitative analysis and development of a conceptual model. *Inflamm Bowel Dis*. 2014;20(3):545-552.
17. Sempere L, Bernabeu P, Cameo J, et al. Gender biases and diagnostic delay in

inflammatory bowel disease: multicenter observational study. *Inflamm Bowel Dis*. 2023;29(12):1886-1894.
18. Umar N, Harvey P, Adderley NJ, Haroon S, Trudgill N. The time to inflammatory bowel disease diagnosis for patients presenting with abdominal symptoms in primary care and its association with emergency hospital admissions and surgery: a retrospective cohort study. *Inflamm Bowel Dis*. 2025;31(1):140-150.
19. Jayasooriya N, Baillie S, Blackwell J, et al; POP-IBD study group. Systematic review with meta-analysis: time to diagnosis and the impact of delayed diagnosis on clinical outcomes in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2023;57(6):635-652.
20. Nguyen VQ, Jiang D, Hoffman SN, et al. Impact of diagnostic delay and associated factors on clinical outcomes in a U.S. inflammatory bowel disease cohort. *Inflamm Bowel Dis*. 2017;23(10):1825-1831.
21. Ley D, Saha S. Menopause and gastrointestinal health and disease. *Nat Rev Gastroenterol Hepatol*. 2025;22(8):556-569. d
22. Lix LM, Graff LA, Walker JR, et al. Longitudinal study of quality of life and psychological functioning for active, fluctuating, and inactive disease patterns in inflammatory bowel disease. *Inflamm Bowel Dis*. 2008;14(11):1575-1584.
23. Moody GA, Mayberry JF. Perceived sexual dysfunction amongst patients with inflammatory bowel disease. *Digestion*. 1993;54(4):256-260.
24. Donaldson EK, Huang V, Ross S, Sydora BC. Experience of menopause in women with inflammatory bowel disease: pilot study. *Climacteric*. 2017;20(6):545-551.
25. Bharadwaj S, Kulkarni G, Shen B. Menstrual cycle, sex hormones in female inflammatory bowel disease patients with and without surgery. *J Dig Dis*. 2015;16(5):245-255.
26. Holroyd CR, Edwards CJ. The effects of hormone replacement therapy on autoimmune disease: rheumatoid arthritis and systemic lupus erythematosus. *Climacteric*. 2009;12(5):378-386.
27. Khan D, Ansar Ahmed S. The immune system is a natural target for estrogen action: opposing effects of estrogen in two prototypical autoimmune diseases. *Front Immunol*. 2016;6:635.
28. Xu L, Huang G, Cong Y, Yu Y, Li Y. Sex-related differences in inflammatory bowel diseases: the potential role of sex hormones. *Inflamm Bowel Dis*. 2022;28(11):1766-1775.
29. Hutson WR, Roehrkasse RL, Wald A. Influence of gender and menopause on gastric emptying and motility. *Gastroenterology*. 1989;96(1):11-17.
30. Moleski SM, Choudhary C. Special considerations for women with IBD. *Gastroenterol Clin North Am*. 2011;40(2):387-398, viii-ix.
31. Sankaran-Walters S, Macal M, Grishina I, et al. Sex differences matter in the gut: effect on mucosal immune activation and inflammation. *Biol Sex Differ*. 2013;4(1):10.
32. Jacenik D, Cygankiewicz AI, Mokrowiecka A, Małecka-Panas E, Fichna J, Krajewska WM. Sex- and age-related estrogen signaling alteration in inflammatory bowel diseases: modulatory role of estrogen receptors. *Int J Mol Sci*. 2019;20(13):3175.
33. Cutolo M, Gotelli E. Complex role of oestrogens in the risk and severity of rheumatoid arthritis in menopause. *RMD Open*. 2023;9(2):e003176.
34. Peters BA, Santoro N, Kaplan RC, Qi Q. Spotlight on the gut microbiome in menopause: current insights. *Int J Womens Health*. 2022;14:1059-1072.
35. Pierdominici M, Maselli A, Varano B, et al. Linking estrogen receptor β expression with inflammatory bowel disease activity. *Oncotarget*. 2015;6(38):40443-40451. d
36. Malutan AM, Dan M, Nicolae C, Carmen M. Proinflammatory and anti-inflammatory cytokine changes related to menopause. *Prz Menopauzalny*. 2014;13(3):162-168.
37. Abildgaard J, Tingstedt J, Zhao Y, et al. Increased systemic inflammation and altered distribution of T-cell subsets in postmenopausal women. *PLoS One*. 2020;15(6):e0235174.
38. Shieh A, Epeldegui M, Karlamangla AS, Greendale GA. Gut permeability, inflammation, and bone density across the menopause transition. *JCI Insight*. 2020;5(2):e134092.
39. Baker JM, Al-Nakkash L, Herbst-Kralovetz MM. Estrogen-gut microbiome axis: physiological and clinical implications. *Maturitas*. 2017;103:45-53.
40. Mavropoulou E, Mechie NC, Knoop R, et al. Association of serum interleukin-6 and soluble interleukin-2-receptor levels with disease activity status in patients with inflammatory bowel disease: a prospective observational study. *PLoS One*. 2020;15(5):e0233811.
41. Kale T, Yoo L, Kroeger E, et al. Menopause and inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis*. 2025;31(12):3443-3449.
42. Nieto MR, Rus MJ, Areal-Quecuty V, Lubián-López DM, Simon-Soro A. Menopausal shift on women's health and microbial niches. *npj Womens Health*. 2025;3(1):3.
43. Santos-Marcos JA, Rangel-Zuñiga OA, Jimenez-Lucena R, et al. Influence of gender and menopausal status on gut microbiota. *Maturitas*. 2018;116:43-53.
44. Peters BA, Lin J, Qi Q, et al. Menopause is associated with an altered gut microbiome and estrobolome, with implications for adverse cardiometabolic risk in the Hispanic community health study/study of Latinos. *mSystems*. 2022;7(3):e0027322.
45. Zhao H, Chen J, Li X, Sun Q, Qin P, Wang Q. Compositional and functional features of the female premenopausal and postmenopausal gut microbiota. *FEBS Lett*. 2019;593(18):2655-2664.
46. Hu S, Ding Q, Zhang W, Kang M, Ma J, Zhao L. Gut microbial beta-glucuronidase: a vital regulator in female estrogen metabolism. *Gut Microbes*. 2023;15(1):2236749.
47. Bhadricha H, Patel V, Singh AK, et al. Increased frequency of Th17 cells and IL-17 levels are associated with low bone mineral density in postmenopausal women. *Sci Rep*. 2021;11(1):16155.
48. Corrêa-Oliveira R, Fachi JL, Vieira A, Sato FT, Vinolo MAR. Regulation of immune cell function by short-chain fatty acids. *Clin Transl Immunology*. 2016;5(4):e73.
49. Gonçalves P, Araújo JR, Di Santo JP. A Cross-talk between microbiota-derived short-chain fatty acids and the host mucosal immune system regulates intestinal homeostasis and inflammatory bowel disease. *Inflamm Bowel Dis*. 2018;24(3):558-572.
50. Kverka M, Stepan JJ. Associations among estrogens, the gut microbiome and osteoporosis. *Curr Osteoporos Rep*. 2024;23(1):2.
51. Park MG, Cho S, Oh MM. Menopausal changes in the microbiome-a review focused on the genitourinary microbiome. *Diagnostics (Basel)*. 2023;13(6):1193.
52. Dothard MI, Allard SM, Gilbert JA. The effects of hormone replacement therapy on the microbiomes of postmenopausal women. *Climacteric*. 2023;26(3):182-192.
53. Triadafilopoulos G, Finlayson M, Grellet C. Bowel dysfunction in postmenopausal women. *Women Health*. 1998;27(4):55-66.
54. Sarnoff RP, Hreinsson JP, Kim J, et al. Sex differences, menses-related symptoms and menopause in disorders of gut-brain interaction. *Neurogastroenterol Motil*. 2025;37(2):e14977.
55. Kreienbuehl AS, Rogler G, Emanuel B, et al. Bone health in patients with inflammatory bowel disease. *Swiss Med Wkly*. 2024;154(6):3407-3407.
56. Attauabi M, Madsen GR, Holm JP, et al. Incidence of osteoporosis and osteopenia in newly diagnosed inflammatory bowel disease: a population-based cohort study. *Inflamm Bowel Dis*. 2025;31(10):2746-2756.
57. van Bodegraven AA, Bravenboer N. Perspective on skeletal health in inflammatory bowel disease. *Osteoporos Int*. 2020;31(4):637-646.
58. Tilg H, Moschen AR, Kaser A, Pines A, Dotan I. Gut, inflammation and osteoporosis: basic and clinical concepts. *Gut*. 2008;57(5):684-694.
59. Kärnsund S, Lo B, Bendtsen F, Holm J, Burisch J. Systematic review of the prevalence and development of osteoporosis or low bone mineral density and its risk factors in patients with inflammatory bowel disease. *World J Gastroenterol*. 2020;26(35):5362-5374.
60. Szafors P, Che H, Barnetche T, et al. Risk of fracture and low bone mineral density in adults with inflammatory bowel diseases. A systematic literature review with meta-analysis. *Osteoporos Int*. 2018;29(11):2389-2397.
61. Chedid VG, Kane SV. Bone health in patients with inflammatory bowel diseases. *J Clin Densitom*. 2020;23(2):182-189.
62. Bernstein CN, Seeger LL, Sayre JW, Anton PA, Artinian L, Shanahan F. Decreased bone density in inflammatory bowel disease is related to corticosteroid use and not disease diagnosis. *J Bone Miner Res*. 1995;10(2):250-256.
63. Caldera F, Kane S, Long M, Hashash JG. AGA Clinical Practice Update on noncolorectal cancer screening and vaccinations in patients with inflammatory bowel disease: expert review. *Clin Gastroenterol Hepatol*. 2025;23(5):695-706.
64. Farraye FA, Melmed GY, Lichtenstein GR, Kane SV. ACG Clinical Guideline: preventive care in inflammatory bowel Disease. *Am J Gastroenterol*. 2017;112(2):241-258. d
65. Pérez-Castrillón JL, Dueñas-Laita A, Brandi ML, et al. Calcifediol is superior to cholecalciferol in improving vitamin D status in postmenopausal women: a randomized trial. *J Bone Miner Res*. 2021;36(10):1967-1978.
66. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis—2020 Update. *Endocr Pract*. 2020;26(suppl 1):1-46.
67. Eastell R, Szulc P. Use of bone turnover markers in postmenopausal osteoporo-

sis. *Lancet Diabetes Endocrinol*. 2017;5(11):908-923.
68. Ratajczak AE, Rychter AM, Zawada A, Dobrowolska A, Krela-Kaźmierczak I. Nutrients in the prevention of osteoporosis in patients with inflammatory bowel diseases. *Nutrients*. 2020;12(6):1702.
69. Yu J, Cao G, Yuan S, Luo C, Yu J, Cai M. Probiotic supplements and bone health in postmenopausal women: a meta-analysis of randomised controlled trials. *BMJ Open*. 2021;11(3):e041393.
70. Wang F, Wei W, Liu PJ. Effects of probiotic supplementation on bone health in postmenopausal women: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. 2024;15:1487998.
71. Vanitchanont M, Vallibhakara SAO, Sophonsritsuk A, Vallibhakara O. Effects of multispecies probiotic supplementation on serum bone turnover markers in postmenopausal women with osteopenia: a randomized, double-blind, placebo-controlled trial. *Nutrients*. 2024;16(3):461.
72. Zeng L, Yu G, Yang K, Hao W, Chen H. The improving effect and safety of probiotic supplements on patients with osteoporosis and osteopenia: a systematic review and meta-analysis of 10 randomized controlled trials. *Evid Based Complement Alternat Med*. 2021;2021:9924410.
73. Weissman S, Sinh P, Mehta TI, et al. Atherosclerotic cardiovascular disease in inflammatory bowel disease: the role of chronic inflammation. *World J Gastrointest Pathophysiol*. 2020;11(5):104-113.
74. Xiao Y, Powell DW, Liu X, Li Q. Cardiovascular manifestations of inflammatory bowel diseases and the underlying pathogenic mechanisms. *Am J Physiol Regul Integr Comp Physiol*. 2023;325(2):R193-R211.
75. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;352(16):1685-1695. d
76. Corral P, Matta MG, Aguilar-Salinas C, et al. Lipoprotein(a) throughout life in women. *Am J Prev Cardiol*. 2024;20:100885.
77. Łykowska-Szuber L, Rychter AM, Dudek M, et al. What links an increased cardiovascular risk and inflammatory bowel disease? A narrative review. *Nutrients*. 2021;13(8):2661.
78. Jung H, Kim JS, Lee KH, et al. Roles of microRNAs in inflammatory bowel disease. *Int J Biol Sci*. 2021;17(8):2112-2123.
79. Argollo M, Gilardi D, Peyrin-Biroulet C, Chabot JF, Peyrin-Biroulet L, Danese S. Comorbidities in inflammatory bowel disease: a call for action. *Lancet Gastroenterol Hepatol*. 2019;4(8):643-654.
80. Robert J. Sex differences in vascular endothelial cells. *Atherosclerosis*. 2023;384:117278.
81. Bigeh A, Sanchez A, Maestas C, Gulati M. Inflammatory bowel disease and the risk for cardiovascular disease: does all inflammation lead to heart disease? *Trends Cardiovasc Med*. 2020;30(8):463-469.
82. Shufelt CL, Manson JE. Menopausal hormone therapy and cardiovascular disease: the role of formulation, dose, and route of delivery. *J Clin Endocrinol Metab*. 2021;106(5):1245-1254.
83. Pinkerton JV. Hormone therapy for postmenopausal women. *N Engl J Med*. 2020;382(5):446-455.
84. Mangione CM, Barry MJ, Nicholson WK, et al; US Preventive Services Task Force. Hormone therapy for the primary prevention of chronic conditions in postmenopausal persons: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2022;328(17):1740-1746.
85. Kane SV, Reddy D. Hormonal replacement therapy after menopause is protective of disease activity in women with inflammatory bowel disease. *Am J Gastroenterol*. 2008;103(5):1193-1196.
86. Freeman M, Lally L, Teigen L, Graziano E, Shivashankar R, Shmidt E. Hormone replacement therapy is associated with disease activity improvement among post-menopausal women with inflammatory bowel disease. *J Clin Med*. 2023;13(1):88.
87. Newman CB, Blaha MJ, Boord JB, et al. Lipid management in patients with endocrine disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2020;105(12):3613-3682.
88. Canonico M. Hormone therapy and risk of venous thromboembolism among postmenopausal women. *Maturitas*. 2015;82(3):304-307.
89. Kreijne JE, Goetgebuer RL, Erler NS, et al; Dutch Initiative on Crohn and Colitis (ICC). Cumulative exposure to immunomodulators increases risk of cervical neoplasia in women with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2023;58(2):207-217.
90. Ananthakrishnan AN, Adler J, Chachu KA, et al; AGA Clinical Guidelines Committee. AGA Clinical Practice Guideline on the role of biomarkers for the management of crohn's disease. *Gastroenterology*. 2023;165(6):1367-1399.
91. Fracas E, Costantino A, Vecchi M, Buoli M. Depressive and anxiety disorders in patients with inflammatory bowel diseases: are there any gender differences? *Int J Environ Res Public Health*. 2023;20(13):6255.
92. Alblooshi S, Taylor M, Gill N. Does menopause elevate the risk for developing depression and anxiety? Results from a systematic review. *Australas Psychiatry*. 2023;31(2):165-173.
93. Bisgaard TH, Allin KH, Elmahdi R, Jess T. The bidirectional risk of inflammatory bowel disease and anxiety or depression: a systematic review and meta-analysis. *Gen Hosp Psychiatry*. 2023;83:109-116.
94. Turek J, Gąsior Ł. Estrogen fluctuations during the menopausal transition are a risk factor for depressive disorders. *Pharmacol Rep*. 2023;75(1):32-43.
95. Gower-Rousseau C, Sarter H, Savoye G, et al; International Programme to Develop New Indexes for Crohn's Disease (IPNIC) group. Validation of the inflammatory bowel disease disability index in a population-based cohort. *Gut*. 2017;66(4):588-596.
96. Chen XL, Zhong LH, Wen Y, et al. Inflammatory bowel disease-specific health-related quality of life instruments: a systematic review of measurement properties. *Health Qual Life Outcomes*. 2017;15(1):177.
97. Davis SP, Bolin LP, Crane PB, Crandell J. Non-pharmacological interventions for anxiety and depression in adults with inflammatory bowel disease: a systematic review and meta-analysis. *Front Psychol*. 2020;11:538741.
98. Szigethy E. Hypnotherapy for inflammatory bowel disease across the lifespan. *Am J Clin Hypn*. 2015;58(1):81-99.
99. Khalili H, Higuchi LM, Ananthakrishnan AN, et al. Hormone therapy increases risk of ulcerative colitis but not Crohn's disease. *Gastroenterology*. 2012;143(5):1199-1206.
100. García Rodríguez LA, González-Pérez A, Johansson S, Wallander MA. Risk factors for inflammatory bowel disease in the general population. *Aliment Pharmacol Ther*. 2005;22(4):309-315.
101. Tseng YT, Chen II, Wang CH. Association of hormone replacement therapy with inflammatory bowel disease risk in women with menopausal disorders: a population-based retrospective cohort study. *Healthcare (Basel)*. 2025;13(5):578.
102. Kim JE, Chang JH, Jeong MJ, et al. A systematic review and meta-analysis of effects of menopausal hormone therapy on cardiovascular diseases. *Sci Rep*. 2020;10(1):20631.