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Risk of Inflammatory Bowel Disease with Oral Contraceptives and Menopausal Hormone Therapy: Current Evidence and Future Directions

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Abstract

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel diseases, are archetypical inflammatory disorders of the gastrointestinal tract with rising incidence worldwide. Although the role of genetic factors in disease development has been highlighted by genome wide association studies, environmental risk factors likely play a pivotal role in development of CD and UC. Prior observational studies have suggested a link between exogenous hormone use and risk of CD and UC. Specifically, studies have shown an association between oral contraceptive use and risk of CD and menopausal hormone therapy and risk of UC. Although the exact mechanism of these associations is largely unknown, a number of hypotheses have been proposed. First, oral estrogen has been shown to modify intestinal permeability, a critical step in the pathophysiology of inflammatory bowel disease. Second, exogenous hormone use through its effect on endogenous levels of hormones may enhance the development of Th1- and Th2-mediated inflammatory diseases. Lastly, recent data have linked modification in the gut microbiome to endogenous levels of androgens, which are also known to be altered with exogenous hormone use and influence the development of autoimmune diseases. This supports the intriguing hypothesis that the gut microbiome lies at the crossroads of pathways linking exogenous hormone use with innate and adaptive immunity. Future studies should therefore focus on bridging these epidemiologic findings to disease pathogenesis through comprehensive understanding of the complex interaction between exogenous hormone use, sex steroid biomarkers, genetic risk loci, and alterations in the intestinal microbial environment in the etiology of CD and UC.

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1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel diseases (IBD), are chronic inflammatory disorders of the gastrointestinal tract in which a barrier normally maintained by adaptive and innate immunity is disrupted. Despite the success of genome wide association (GWA) studies in identifying more than 100 risk loci associated with UC and CD (1, 2), the pathogenesis of the two diseases remains largely unknown. It is estimated the risk contribution from these genetic predispositions is less than 25% (3), highlighting the importance of environment in the development of incident IBD. This is further illustrated by rapid rise in CD and UC incidence in the U.S. and developing countries that have witnessed a dramatic 'westernization' of lifestyle. More notably, studies have identified an incidence of disease in immigrants to developed countries that exceeds that of their country of origin (4). Recently a number of prospective studies have suggested an association between exogenous hormone use in the form of oral contraceptive and menopausal hormone therapy and risk of CD and UC(5, 6). In this paper, I will review the current data on the association between exogenous hormone use and risk of IBD and discuss how this information may impact clinical practice.

2. Epidemiologic Evidence

2a. Oral Contraceptives and Risk of CD and UC

The association between oral contraceptive use and intestinal inflammation including CD and UC were first reported in the form of case reports starting in late in 1960s (7–9). In 1984, Rhodes and colleagues showed that the prevalence of oral contraceptive use was higher among patients with colonic CD compared to age-matched women with small intestinal CD or UC (10). Interestingly, some of the early case series demonstrated resolution of CD upon discontinuation of oral contraceptive use (11). Since then, a number of studies have evaluated the association between oral contraceptive use and risk of CD and UC (12). A meta-analysis of nearly 14 studies published by Cornish and colleagues in 2008 showed that current use of oral contraceptives is associated with a nearly 50% increase in risk of CD (RR= 1.46, 95% CI 1.26–1.70) (12). The risk appeared to increase with longer duration of use and diminished following discontinuation. In contrast, although there also appeared to be an increase risk of UC with current use of oral contraceptives (RR= 1.53, 95% CI 1.21–1.94), the risk significantly attenuated and was not longer statistically significant after adjusting for smoking (RR= 1.28, 95% CI 1.06–1.54). More recently, these data have been replicated in two large prospective cohorts of US women, the Nurses' Health Study (NHS) and NHSII (6). Specifically, in a pooled analysis of NHS and NHSII, current use of oral contraceptives was associated with an increased risk of CD (HR = 2.82, 95% CI 1.65 to 4.82) but not UC (HR = 1.22, 95% CI 0.74–2.07). Because of the relatively large size (> 200,000 women), its prospective design, and detailed data on exogenous hormone use, which are some of the primary exposures of these cohorts, this study provided further convincing data linking oral contraceptives to CD. In addition, this study did not find an association between other reproductive factors including parity, age at menarche, and age at first child birth, which may also be closely linked to use of oral contraceptive use, and risk of CD.

2b. Menopausal Hormone Therapy and Risk of CD and UC

Data specifically relating the use of menopausal hormone therapy in postmenopausal women to risk of CD and UC are sparse. A case-control study (13) using the United Kingdom General Practice Research Database assessed the relationship between a number of risk factors, including hormone use and incidence of IBD and found a positive statistically significant association with CD but not UC. However, the study was limited by a small number of cases (7 for UC and 12 for CD) among hormone users and short follow up (mean 2.2 years). In contrast, in a large prospective cohort of US women enrolled in NHS, current use of menopausal hormone therapy was associated with increased risk of UC (HR = 1.71, 95% CI 1.07–2.74) but not CD (HR = 1.19, 95% CI 0.78–1.82) (5). The risk appeared to increase with longer duration of use and diminished following discontinuation of use.

3. Plausible Biologic Mechanisms

Although these findings are compelling, the precise mechanism by which oral contraceptives mediates risk of CD is unknown. Experimental data suggest that estrogen may modulate the mucosal immune system and maintain intestinal barrier function (14, 15). Similarly, many of the CD genes identified through GWA studies including *IRGM1, ATG16L1, NOD2, PTPN2, and PRDM1* appear to have functional consequences that are relevant to regulation of the innate immune system and maintenance of intestinal barrier function. As such, the effects of oral contraceptives may be plausibly influenced by a host genetic background, which may impact the gut microbiota, host immune systems, and intestinal barrier function.

The association between oral contraceptives and CD may also be mediated through modulation of endogenous sex steroid hormones. Oral contraceptives, irrespective of the specific formulation, are associated with a 60% increase in endogenous estrogen and a 2–3 fold increase in sex-hormone binding globulin (SHBG) (16, 17). In contrast, oral contraceptives are associated with a 50% decrease in testosterone and dehydroepiandrosterone sulfate (DHEAS), a metabolic intermediate in androgen biosynthesis. Testosterone has been shown to modulate immune function, including cytokine production. In animal models, endogenous levels of testosterone are linked to reduction in expression of Toll-like receptor 4 (TLR4) on macrophages, which play a fundamental role in pathogen recognition and innate immunity (18). In support of this hypothesis, a recent nested case-control study from the NHS and NHSII cohorts, demonstrated an inverse association between endogenous circulating levels of testosterone and risk of CD (19). Interestingly, this study showed that exogenous hormone use appear to modify the effect of testosterone on risk of CD suggesting that the effect of hormone use on risk of CD may be mediated by changes in endogenous levels of testosterone.

Finally, there is also data linking endogenous and exogenous sex hormone to human microbiota. Available data suggest that exogenous estrogen is associated with changes in the vaginal flora, characterized by an increase in *lactobacilli* species with a concomitant decrease in vaginal infections (20–22). Oral contraceptives are also associated with an increase in certain *Candida* and *Prevotella* species in oral flora with a resultant increase in risk of periodontitis (23). In addition, recent animal data suggest that gut commensal

microbes may modulate levels of endogenous testosterone, leading to development of autoimmune diseases.(24) Thus, the observed association between exogenous hormone use and endogenous testosterone and development of CD may be biologically mediated by a complex interaction between endogenous hormones, the gut microbiome, and immune function. Of note, there is also data suggesting a possible role for microvascular ischemia in etiology of CD(25, 26), which may in turn suggest that oral contraceptives through their effect in inducing microvascular ischemia increase the risk of CD.

Although compared to oral contraceptives, the association between menopausal hormone therapy and risk of CD and UC appears paradoxical, a number of significant difference are worth noting. First, there are significant differences in the dosage and formulation of hormones in oral contraceptives as compared with menopausal hormone therapy. Second, the effect of exogenous hormones may differ according to a woman's age or endogenous hormonal milieu (e.g. the high estrogen environment of premenopause or estrogen-depleted state of postmenopause). Finally, although our understanding of the pathogenesis of UC and CD remains incomplete, the discovery of distinct genetic susceptibility loci for both diseases points to potential diverging biological pathways that may be differentially influenced by exogenous hormones (3, 27). For example, studies have demonstrated that UC and CD have immunologically distinct gastrointestinal mucosal cytokine profiles, with mucosal inflammation in CD primarily mediated by Th1-related cytokines and UC mediated by Th2-related cytokines. (28–31) Estrogen has been implicated in the etiology and progression of other Th2-mediated diseases such as rheumatoid arthritis and systemic lupus erythematous, (32, 33) through enhancing cell proliferation and the humoral immune system.

4. Future Directions and Clinical Recommendations

Beyond smoking, perhaps the most consistent environmental risk factor for CD is the use of oral contraceptives. However, as CD is a relatively rare complex disorder, the population-level impact of findings from prior epidemiologic studies is relatively low, making it difficult to provide rationale for clinical recommendations about oral contraceptive use even among women at high-risk (e.g. family history of CD). Similarly, because of the relatively small contribution of menopausal hormone therapy to risk of UC as well as many cogent reasons for women to minimize their use of postmenopausal hormones given their potential for adverse effects (34), results from prior studies have more mechanistic implications.

In the absence of clear biologic rationale, previous epidemiological findings are sometimes dismissed as "mere associations", therefore future studies should focus on bridging epidemiologic correlations to disease causation through comprehensive understanding of the complex interaction between oral contraceptives, sex steroid biomarkers, genetic risk loci, and alterations in the intestinal microbial environment in the etiology of CD and UC. Finally, a specific role of oral contraceptives on progression, rather than the etiology of CD and UC is unclear. The few prior studies that have investigated the link between oral contraceptive use and CD and UC progression have had significant limitations including retrospective design (35), small sample size (35, 36), and limited ascertainment of oral contraceptive exposure (35–37). In addition, because of a secular trend in the type and dose of oral contraceptive use (38), more recent studies to evaluate the effect of newer

generations oral contraceptives on CD and UC progression are needed. Such studies will help inform clinical recommendations about use of oral contraceptives or menopausal hormone therapy in patients with established disease.

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Key Points

Prior studies have shown a consistent association between oral contraceptive use and risk of CD.

Menopausal hormone therapy may be associated with increased risk of UC.

The effect of oral contraceptive and menopausal hormone therapy on CD and UC progression is unclear.